

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

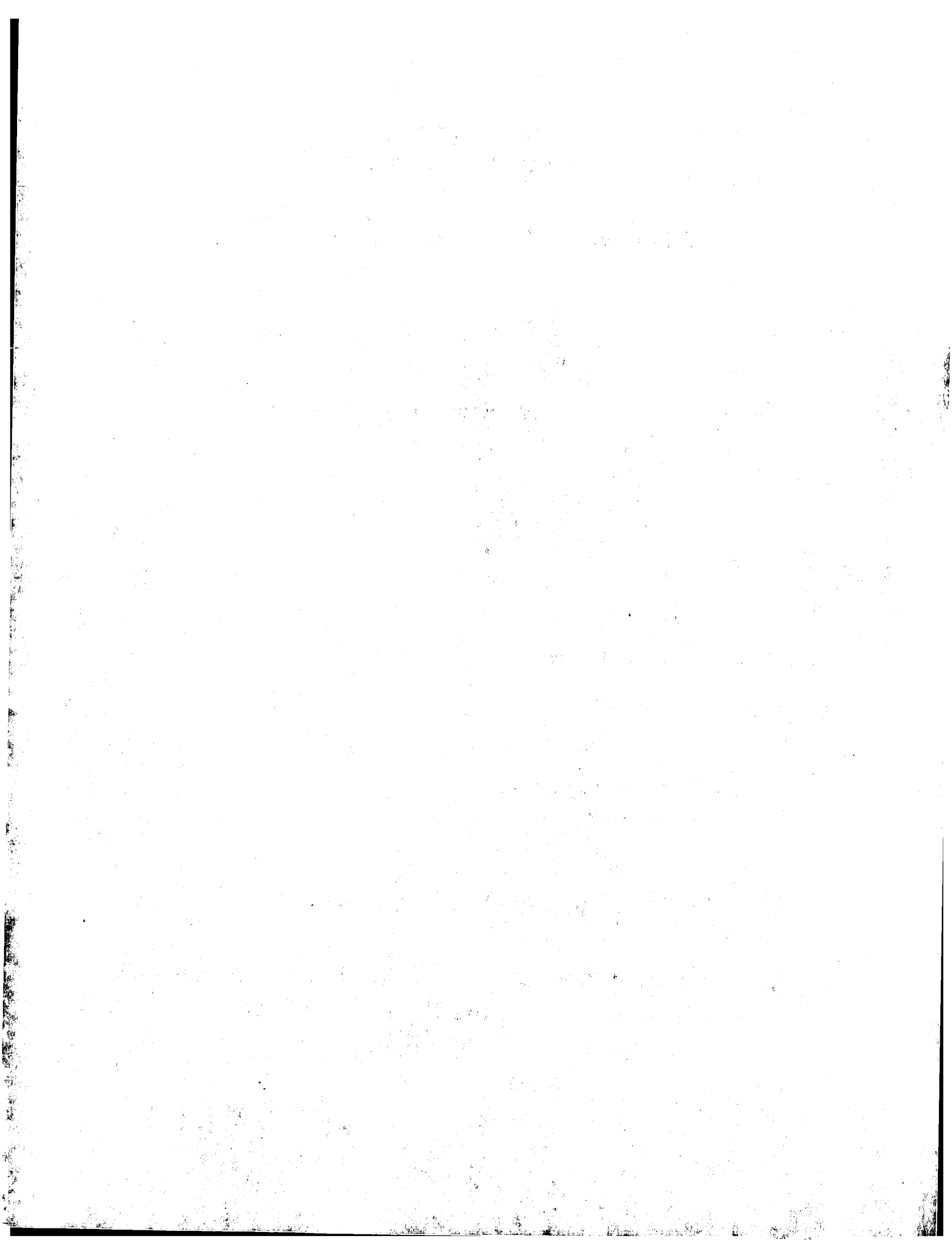
Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



(11) (A) No. 994338

(45) ISSUED 760803

(52) CLASS 260-235.95
C.R. CL. 260-280
260-380

(19) (CA)

CANADIAN PATENT

(54)

**COMPOSITIONS CONTAINING HETEROCYCLIC
BRONCHODILATING AGENTS**

(70)

**Williams, Haydn W.R. and Rooney, Clarence S.,
Canada****Granted to Merck Sharp & Dohme (U.S.A.) Corp., U.S.A., doing
business as Laboratoires Merck Frosst Laboratories,
Canada**

(21)

APPLICATION No. 182,016

(22)

FILED 730925

(30)

PRIORITY DATE**No. OF CLAIMS****16 - No drawing**

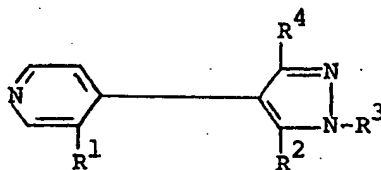
SUBSTITUTE
REMPLACEMENT

SECTION is not Present
Cette Section est Absente

994338

1 This invention is concerned with agents that effec-
 2 tively inhibit bronchial constriction and a method for treat-
 3 ing animals to overcome bronchial constriction induced by
 4 histamine or other bronchial constricting substances. The
 5 agents found useful in the method and formulations of this
 6 invention have been found to be superior to most bronchodi-
 7 lating agents because they have relatively low chronotropic
 8 effect. Additionally, some of the compounds also exhibit
 9 useful hypotensive properties.

10 The agents useful in the method and formulations
 11 of this invention are 4-(4-pyridyl)pyrazole compounds which
 12 optionally can carry one or more of a variety of substituents
 13 in either or both of the heterocyclic nuclei. Products that
 14 have been found to be particularly effective have the struc-
 15 ture



I

17 and pharmacologically acceptable salts thereof wherein R¹
 18 represents hydrogen, nitro, amino, acetylamino, mono- or di-
 19 alkylamino, cyano, phenyl, hydroxy, alkoxy, or halo, prefer-
 20 ably chloro; R² represents hydrogen, halogen, preferably
 21 chloro, alkyl, hydroxy, alkoxy, cyano, amino, acetylamino,
 22 mono- or di-alkylamino, phenyl, furyl, 4-pyridyl, 1-pyrrolyl
 23 or mono- or di-C₁₋₃ alkyl-1-pyrrolyl; R³ represents hydrogen,
 24 alkyl either straight or branched chain and having from 1-5
 25 carbon atoms, alkenyl, alkynyl, C₃₋₁₀ cycloalkyl, preferably
 26 adamantyl, haloalkyl, preferably polyfluoroalkyl, alkoxy-
 27 alkyl, hydroxyalkyl, dialkylaminoalkyl, (4-pyridyl)-C₁₋₃



1 alkyl, alkoxycarbonylalkyl, mono- or di-alkylaminocarbonyl-
 2 alkyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl,
 3 4-alkylpiperazinylcarbonyl, piperidinocarbonyl, N-alkylthio-
 4 carbamoyl, phenyl, amidino or mono-, di- or tri-alkyl sub-
 5 stituted amidino, 2-imidazolin-2-yl or 1-C₁₋₅ alkyl substitu-
 6 ted 2-imidazolin-2-yl, 2-, 3- or 4-pyridyl, 2-(3,4,5,6-tetra-
 7 hydropyrimidinyl), 2-(3,4-dihydro-1,3-thiazolyl), and 2-(5,6-
 8 dihydro-4(H)-1,3-thiazinyl); R² and R³ can be linked together
 9 to form with the pyrazole nucleus to which they are attached
 10 a 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl, a 4-C₁₋₃
 11 alkyl substituted 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-
 12 3-yl or a 6,7-dihydro-5(4H)-oxopyrazolo[1,5-a]pyrimidin-3-
 13 yl; and R⁴ represents hydrogen and C₁₋₃ alkyl.

14 In the above definitions, unless otherwise indi-
 15 cated, the alkyl and alkoxy groups have from 1 to 3 carbon
 16 atoms and the alkenyl and alkynyl groups have from 3 to 5
 17 carbon atoms.

18 Products having the above structure wherein R¹
 19 represents hydrogen have been found to be particularly effec-
 20 tive agents for use in the method and formulations of this
 21 invention. Among the active agents in this subgroup of com-
 22 pounds those products wherein R² represents hydrogen, amino,
 23 acetylamino, mono- or di-alkylamino or 1-pyrrolyl and R³
 24 represents hydrogen, straight or branched chain alkyl, alkoxy-
 25 alkyl, mono- or di-alkylcarbamoyl, 2-imidazolin-2-yl or a
 26 1-alkyl-2-imidazolin-2-yl and R⁴ is hydrogen or alkyl have
 27 been found to exhibit particularly desirable properties.
 28 The most active products for use in the method and formula-
 29 tions of this invention are

- 30 1. Products having structural formula I wherein
 31 R¹, R² and R⁴ each represent hydrogen, and R³
 32 is 2-imidazolin-2-yl or a 1-alkyl-2-imidazol-
 33 in-2-yl, particularly 1-methyl(or ethyl)-2-
 34 imidazolin-2-yl,

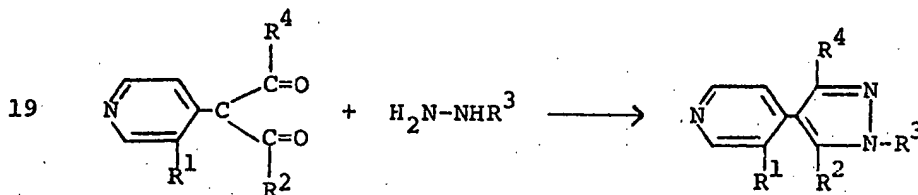
994338

2. Products having structural formula I wherein R^1 and R^4 each represent hydrogen, R^3 is alkyl, preferably methyl and R^2 is 1-pyrrolyl or mono- or di-alkyl-1-pyrrolyl, acetylamino, di-alkyl-amino preferably dimethylamino or alkylamino preferably ethylamino, and

3. Products having structural formula I wherein R^1 , R^2 and R^4 each represents hydrogen and R^3 is alkyl, alkoxyalkyl, dialkylcarbamoyl preferably dimethylcarbamoyl, or amidino.

While known methods can be employed to prepare the 4-(4-pyridyl)pyrazole bronchodilating agents, the following procedures were found to be particularly suitable for making the various products employed in the method and formulation of this invention.

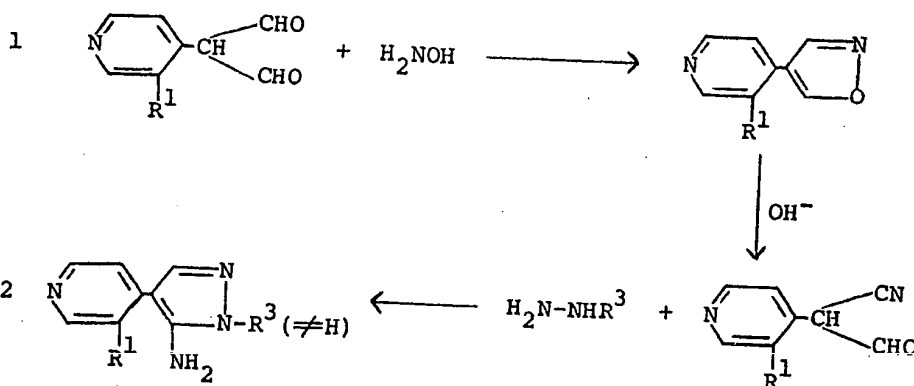
Most of the 4-(4-pyridyl)pyrazole products were prepared by condensing a β -dicarbonyl compound with a hydrazine derivative as schematically depicted below:



The above process conveniently is carried out at between ambient to about 100° C. in one of the following solvents: ethanol (usually with a drop of acetic acid as catalyst), dilute hydrochloric acid, 85% phosphoric acid or by an azeotropic procedure (benzene containing slightly more than 2 equivalents of acetic acid).

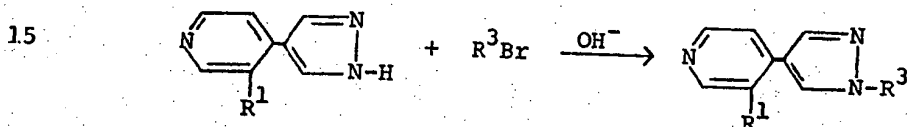
4-(4-Pyridyl)-5-aminopyrazoles having a substituent in the 1-position are conveniently made by the following reaction:

994338



3 The first step is carried out by the reaction of the pyridine
 4 malondialdehyde and hydroxylamine preferably with moderate
 5 heating to give the 4-(4-pyridyl)isoxazole which, upon treat-
 6 ment with base, provides 2-formyl-2-(4-pyridyl)acetonitrile.
 7 The intermediate acetonitrile product then is reacted with
 8 the selected hydrazine in the presence of benzene and acetic
 9 acid at reflux temperature yielding the 1-substituted-4-(4-
 10 pyridyl)pyrazole.

11 Alternatively, the 4-(4-pyridyl)pyrazole can be
 12 alkylated in the 1-position by employing known alkylating
 13 procedures and agents as indicated by the following reaction
 14 schema:



16 This alkylation conveniently is carried out at room tempera-
 17 ture in the presence of a base, suitably sodium ethoxide.
 18 Should a substituent be present in the 3(5)-position, alkyl-
 19 ation may give two products.

20 Substituents on the pyridyl ring or the pyrazole
 21 ring can be modified by known methods. For example, a nitro
 22 can be reduced to an amino, the amino converted to a cyano,
 23 acetylamino, mono- or di-alkylamino, or an amino substituent

994338

1 can be replaced by chloro or hydroxy and the hydroxy conver-
2 ted to an alkoxy substituent or an ester group converted to
3 an amide, all of these conversions being effected by known
4 procedures.

5 Suitable pharmacologically acceptable salts of
6 product I prepared by conventional methods are acid addition
7 salts derived from inorganic acids for example hydrochlor-
8 ides, hydrobromides, phosphates, or sulfates or salts de-
9 rived from organic acids, for example, fumarates, oxalates,
10 lactates, malates, maleates, isethionates, formates, acetates,
11 succinates, tartrates, salicylates, citrates, phenylace-
12 tates, benzoates, p-toluenesulfonates, pamoates and other
13 salts such as those that provide relatively insoluble pro-
14 ducts that afford a slow release of the active material, for
15 example, a 1,1'-methylene-bis(2-hydroxy-3-naphthoate) and
16 the like.

17 The 4-(4-pyridyl)pyrazoles can be administered in
18 the method of this invention in formulations suitable for
19 oral or parenteral administration or in aerosol preparations.
20 Intravenous or intraduodenal doses in the range of between
21 about 2 mg./kg. to about 75 mg./kg. provided protection at
22 the ED₅₀ level against the induced bronchoconstriction in
23 most animals challenged. Those products that also exhibi-
24 ted hypotensive properties were effective within the same
25 dosage range.

26 The 4-(4-pyridyl)pyrazoles can be formulated by
27 conventional means with pharmaceutical carriers and may, if
28 desired, be combined with other desired pharmacologically
29 active compounds. Capsules, tablets, or liquid preparations
30 can be prepared for oral administration, solutions or sus-
31 pensions of the active ingredient can be prepared for

994338

1 parenteral administration and aerosols containing the active
2 ingredient can be prepared by conventional methods for topi-
3 cal application or application to mucous membranes. For ex-
4 ample, a capsule can be prepared by conventional methods em-
5 ploying lactose as an excipient and containing per unit
6 dosage 5-25 mg. of active compound, although unit dosages
7 can range between about 5-100 mg. for administration as pre-
8 scribed by the physician.

9 The following examples describe the preparation
10 of certain representative 4-(4-pyridyl)pyrazole compounds
11 that have been found to be effective bronchodilating agents
12 in the method and formulations of this invention.

13 EXAMPLE 1

14 1-Methyl-4-(4-pyridyl)-pyrazole

15 A mixture of 4-pyridylmalondialdehyde (10 mmole),
16 methylhydrazine (10.3 mmole) and 85% phosphoric acid (25
17 ml.) is heated on a steam bath for 5 hours. The reaction
18 mixture then is poured into ice water and made basic with
19 ammonium hydroxide to precipitate the crude product (44%
20 yield). After isolation by extraction with ethyl acetate
21 and recrystallization from petroleum ether there is obtained
22 purified 1-methyl-4-(4-pyridyl)-pyrazole, m.p. 76-78° C.

23 Analysis calculated for $C_9H_9N_3$:

24 C, 67.90; H, 5.70; N, 26.40;

25 Found: C, 67.86; H, 5.64; N, 26.29.

26 EXAMPLE 2

27 1-t-Butyl-4-(4-pyridyl)-pyrazole hydrochloride

28 A mixture of 4-pyridylmalondialdehyde (1.49 g.,
29 10 mmole), t-butylhydrazine hydrochloride (1.62 g., 13 mmole),
30 sodium acetate trihydrate (1.8 g.), acetic acid (1.3 ml.) and
31 benzene (40 ml.) is heated under reflux under a Dean Stark
32 trap for 4 hours by which time 1.1 ml. of water is collected.

994338

1 The reaction mixture is evaporated under reduced pressure
2 and the residue is made basic with 5N sodium hydroxide solu-
3 tion, extracted with ethyl acetate and dried over magnesium
4 sulfate. The dried extract is evaporated to afford 2.1 g.
5 of free base, which is taken up in a small volume of isopro-
6 panol and acidified with ethanolic hydrogen chloride to
7 yield 1.9 g., (80%), of 1-t-butyl-4-(4-pyridyl)-pyrazole
8 hydrochloride, m.p. 214-216° C. Recrystallization of the
9 salt from a mixture of isopropanol and ether raises its
10 melting point to 215-216° C.

11 Analysis calculated for $C_{12}H_{15}N_3 \cdot HCl$:
12 C, 60.63; H, 6.78; Cl, 14.91; N, 17.68;
13 Found: C, 60.82; H, 7.31; Cl, 14.89; N, 17.37.

14 EXAMPLE 3

15 1-Isobutyl-4-(4-pyridyl)-pyrazole hydrogen maleate

16 By replacing t-butylhydrazine hydrochloride with
17 isobutylhydrazine hydrochloride in Example 2, there is ob-
18 tained 1-isobutyl-4-(4-pyridyl)-pyrazole. After the reac-
19 tion mixture residue is made basic, the crude base is iso-
20 lated by extraction with ethyl acetate, and then dissolved
21 in isopropanol. One equivalent of maleic acid is added to
22 the hot solution and on cooling, the maleate salt of the
23 product crystallizes out in 63% yield, m.p. 137-139° C. Upon
24 further purification by recrystallization from the same sol-
25 vent the salt melts at 137-138° C.

26 Analysis calculated for $C_{12}H_{15}N_3 \cdot C_4H_4O_4$:
27 C, 60.56; H, 6.03; N, 13.24;
28 Found: C, 60.47; H, 5.86; N, 13.47.

29 EXAMPLE 4

30 1-Allyl-4-(4-pyridyl)-pyrazole hydrochloride

31 To a solution of sodium (322 mg., 14 mmole) in

994338

1 ethanol (25 ml.) is added 4-(4-pyridyl)-pyrazole (2.03 g.,
2 14 mmole), followed by allyl bromide (1.7 g., 14 mmole).
3 The mixture is stirred at room temperature for 2 days and
4 evaporated to dryness. The residue is leached with ether,
5 and to the ethereal solution is added ethanolic hydrogen
6 chloride. The precipitated solid is recrystallized from a
7 mixture of isopropanol and ether to afford 1-allyl-4-(4-
8 pyridyl)-pyrazole hydrochloride (1.1 g., 32%), m.p. 208-210°
9 C. Further recrystallization of the solid raises its melt-
10 ing point to 210-211° C.

11 Analysis calculated for $C_{11}H_{11}N_3 \cdot HCl$:
12 C, 59.60; H, 5.45; Cl, 15.99; N, 18.95;
13 Found: C, 59.77; H, 5.60; Cl, 16.27; N, 19.07.

14 EXAMPLE 5

15 1-(1-Adamantyl)-4-(4-pyridyl)-pyrazole
16 hydrochloride monohydrate

17 By replacing the t-butylhydrazine hydrochloride
18 with 1-adamantylhydrazine hydrochloride in Example 2, there
19 is obtained 1-(1-adamantyl)-4-(4-pyridyl)-pyrazole hydro-
20 chloride monohydrate in 44% yield, m.p. 315-320° C.

21 Analysis calculated for $C_{18}H_{21}N_3 \cdot HCl \cdot H_2O$:
22 C, 64.75; H, 7.24; Cl, 10.62; N, 12.59;
23 Found: C, 64.89; H, 7.40; Cl, 10.73; N, 12.49.

24 EXAMPLE 6

25 1-Methyl-4-(4-pyridyl)-5-amino-pyrazole hydrochloride
26 Step A: Preparation of 2-Formyl-2-(4-pyridyl)-acetonitrile
27 4-Pyridine malondialdehyde (29.8 g., 0.2 mole) is
28 added to a solution of hydroxylamine hydrochloride (16.0 g.,
29 0.23 mole) in water (500 ml.) and the mixture is heated at
30 65-70° C. for 2 hours. When cool, the solution is made
31 basic with 10% sodium carbonate solution, the crude 4-(4-

994338

1 pyridyl)-isoxazole is filtered off, washed with water and
2 drained on the filter. The solid is suspended in water
3 (500 ml.) and the suspension made basic with 5N sodium
4 hydroxide (50 ml.). The suspension is heated briefly until
5 solution occurs, then it is cooled to room temperature and
6 acidified with acetic acid. The crude product is collected,
7 washed with water and dried, yielding 25.4 g. (86%) of pro-
8 duct as a pale pinkish powder. Following purification by
9 dissolution in dilute sodium hydroxide, treatment of the
10 solution with charcoal, and then slow acidification of the
11 filtrate with acetic acid, a crystalline solid is obtained
12 which decomposes above 320° C.

13 Analysis calculated for $C_8H_6N_2O$:

14 C, 65.74; H, 4.14; N, 19.17;

15 Found: C, 66.14; H, 4.35; N, 19.04.

16 Step B: Preparation of 1-Methyl-4-(4-pyridyl)-5-amino-pyra-
17 zole hydrochloride

18 2-Formyl-2-(4-pyridyl)-acetonitrile (10.5 g., 72
19 mmole) is suspended in a mixture of benzene (96 ml.) and
20 acetic acid (9.0 ml.), and to the suspension is added methyl-
21 hydrazine (4.33 g., 93.5 mmole). The reaction mixture is
22 heated under reflux for 4-1/2 hours and water formed in the
23 reaction is collected in a Dean-Stark trap. After standing
24 at ambient temperature overnight, the crystalline solid is
25 collected, dissolved in ethanol and the hydrochloride salt
26 is formed by adding a slight excess of ethanolic hydrogen
27 chloride solution. The product (6.3 g.) is purified by re-
28 crystallization from ethanol and then has a melting point of
29 295-300° C.

30 Analysis calculated for $C_9H_{10}N_4 \cdot HCl$:

31 C, 51.31; H, 5.26; N, 26.60; Cl, 16.83;

32 Found: C, 50.97; H, 5.10; N, 26.81; Cl, 17.10.

994338

EXAMPLE 73(5)-Amino-4-(4-pyridyl)-pyrazole hydrochloride

By replacing methylhydrazine employed in Example 6, Step B, with 85% hydrazine hydrate there is obtained 3(5)-amino-4-(4-pyridyl)-pyrazole hydrochloride in 28% yield, m.p. 290-293° C. after recrystallization from a mixture of methanol and ethanol.

Analysis calculated for $C_8H_8N_4 \cdot HCl$:

C, 48.86; H, 4.61; Cl, 18.03; N, 28.49;

Found: C, 48.65; H, 4.73; Cl, 17.92; N, 28.40.

EXAMPLE 81-Methyl-4-(4-pyridyl)-5-chloro-pyrazole hydrochloride

To a solution of 1-methyl-4-(4-pyridyl)-5-amino-pyrazole hydrochloride, prepared as described in Example 6, (421 mg., 2 mmole) in 5N hydrochloric acid (2 ml.) cooled in an ice bath, there is added finely powdered sodium nitrite (138 mg., 2 mmole) in small portions with stirring. The solution is stirred at 0-5° C. for 30 minutes to provide the diazonium salt. Meanwhile a hot (50-60° C.) solution of cupric sulfate pentahydrate (398 mg., 2 mmole) and sodium chloride (238 mg., 4 mmole) in water (1.3 ml.) is saturated with sulfur dioxide and cooled. The cuprous chloride is filtered off, washed with a little cold water and then dissolved in 5N hydrochloric acid (0.7 ml.) on a steam bath. The cuprous chloride solution is removed from the steam bath and the diazonium solution is added slowly with stirring. After stirring the mixture on a steam bath for 10 minutes, it is allowed to cool to ambient temperature, then made basic with ammonium hydroxide and the crude product isolated by extraction with ether (3 x 7 ml.). The oily crude product is dissolved in isopropanol (2 ml.), and a

994338

1 slight excess of ethanolic hydrogen chloride is added to
2 form 236 mg. of the hydrochloride, m.p. 275-278° C. (dec.).
3 The pure product separates from alcohol in pale yellow
4 crystals, m.p. 276.5-278.5° C. (dec.).

5 Analysis calculated for $C_9H_8ClN_3 \cdot HCl$:

6 C, 46.98; H, 3.94; Cl, 30.82; N, 18.26;

7 Found: C, 46.69; H, 4.05; Cl, 30.58; N, 18.09.

8 EXAMPLE 9

9 1-Methyl-4-(4-pyridyl)-5-hydroxy-pyrazole hydrochloride
10 1-Methyl-4-(4-pyridyl)-5-amino-pyrazole (348 mg.,
11 2 mmole), prepared as described in Example 6, is added to
12 trifluoroacetic acid (2 ml.), and to the stirred mixture
13 cooled in an ice bath is added finely powdered sodium ni-
14 trite (150 mg., 2.17 mmole) in small portions over 15 min-
15 utes. The mixture is stirred in the ice bath for 15 min-
16 utes, and then at ambient temperature for 15 minutes before
17 it is poured slowly into boiling 10% sulfuric acid (7 ml.).
18 The solution is boiled for 15 minutes, and then cooled to
19 ambient temperature. After partial neutralization with 10N
20 sodium hydroxide solution (with cooling), basification of
21 the reaction mixture is completed with solid sodium carbon-
22 ate. The crude product (197 mg.), is isolated by continuous
23 extraction with methylene chloride for 24 hours, and puri-
24 fied by chromatography on silica gel using ethyl acetate as
25 the solvent. The product is contained in the first fraction
26 to be eluted: the free base is dissolved in isopropanol (1
27 ml.), and a slight excess of ethanolic hydrogen chloride is
28 added to precipitate the hydrochloride salt. The solid
29 (100 mg.) is recrystallized from a mixture of ethanol and
30 isopropanol affording 61 mg. of product as slightly hygro-
31 scopic crystals, m.p. 185-195° C. (dec.).

994338

1 Analysis calculated for $C_9H_9N_3O \cdot HCl$:

2 C, 51.07; H, 4.76; Cl, 16.75; N, 19.85;

3 Found: C, 50.47; H, 5.58; Cl, 16.40; N, 19.96.

4 EXAMPLE 10

5 1-Methyl-4-(4-pyridyl)-5-cyano-pyrazole hydrochloride

6 1-Methyl-4-(4-pyridyl)-5-amino-pyrazole (348 mg.,
7 2 mmole), prepared as described in Example 6, in trifluoro-
8 acetic acid (2 ml.) at 0-5° C. is diazotized by the addition,
9 in small portions, of finely powdered sodium nitrite (150 mg.,
10 2.17 mmole). After stirring the mixture for one hour at am-
11 bient temperature, the solution is diluted with water (4 ml.)
12 and partially neutralized with sodium carbonate (0.5 g.)
13 added in small portions with stirring. This solution then
14 is added slowly to a solution of cuprous cyanide (896 mg.,
15 10 mmole) and sodium cyanide (1.416 g., 24 mmole) in water
16 (6 ml.) at 40° C. The reaction mixture is kept at 40° C.
17 for 15 minutes, and then adjusted to ca. pH 10 with ammonium
18 hydroxide. The crude free base is isolated by ether extrac-
19 tion and converted to a hydrochloride salt by addition of
20 an ethanolic hydrogen chloride solution, yielding 55 mg.
21 (12-1/2%) of product, m.p. 255-260° C. Following further
22 purification by recrystallization from alcohol, the product
23 melts at 261-263° C. as slightly hygroscopic crystals.

24 Analysis calculated for $C_{10}H_8N_4 \cdot HCl$:

25 C, 54.43; H, 4.11; Cl, 16.07; N, 25.39;

26 Found: C, 53.90; H, 4.53; Cl, 16.25; N, 25.11.

27 EXAMPLE 11

28 1-Methyl-4-(4-pyridyl)-5-acetamido-pyrazole hydrochloride

29 A mixture of 1-methyl-4-(4-pyridyl)-5-amino-pyra-
30 zole (1.0 g., 5.75 mmole), prepared as described in Example
31 6, and acetic anhydride (5 ml.) is heated on a steam bath

994338

1 for 3 hours and then evaporated under vacuum. The residue
2 is dissolved in isopropanol and ethanolic hydrogen chloride
3 is added. Precipitation of the product is completed by
4 adding dry ether and following recrystallization from etha-
5 nol, there is obtained 520 mg. (36%) of product, m.p. 298-
6 301° C.

7 Analysis calculated for $C_{11}H_{12}N_4O \cdot HCl$:

8 C, 52.28; H, 5.18; Cl, 14.03; N, 22.17;

9 Found: C, 51.97; H, 5.17; Cl, 13.88; N, 22.24.

10 EXAMPLE 12

11 1-Methyl-4-(4-pyridyl)-5-dimethylamino-pyrazole

12 A mixture of 1-methyl-4-(4-pyridyl)-5-amino-pyra-
13 zole (2.98 g., 20 mmole), prepared as described in Example
14 6, 88% formic acid (5 ml.) and 40% formaldehyde (10 ml.) is
15 heated under reflux in an oil bath at 120-130° C. for 40
16 hours, and then evaporated under reduced pressure. The
17 residue is dissolved in a little water, the solution made
18 basic with ammonium hydroxide and the product extracted with
19 ethyl acetate. Evaporation of the ethyl acetate affords
20 crude product which, on recrystallization from water, gives
21 1.65 g. (41%) of purified product in the form of colorless
22 needles, m.p. 121.5-123° C.

23 Analysis calculated for $C_{11}H_{14}N_4$:

24 C, 65.32; H, 6.98; N, 27.70;

25 Found: C, 65.33; H, 7.00; N, 28.21.

26 EXAMPLE 13

27 1-t-Butyl-4-(4-pyridyl)-5-amino-pyrazole
28 hydrochloride monohydrate

29 By replacing methylhydrazine employed in Example
30 6 with an equivalent quantity of t-butylhydrazine hydro-
31 chloride plus an equivalent amount of sodium acetate, there
32 is obtained 1-t-butyl-4-(4-pyridyl)-5-amino-pyrazole. The

994338

1 free base is isolated by evaporating the reaction mixture to
2 dryness, dissolving the residual oil in water, adding ammon-
3 ium hydroxide and extracting with ethyl acetate. The crude
4 base obtained by evaporation of the extract is dissolved in
5 isopropanol and a slight excess of ethanolic hydrogen chlor-
6 ide is added. The solid is collected and recrystallized
7 from a mixture of isopropanol and ether containing charcoal
8 giving product, m.p. 230° C. The crystals are hydrated.

9 Analysis calculated for $C_{12}H_{16}N_4 \cdot HCl \cdot H_2O$:
10 C, 53.23; H, 7.07; Cl, 13.09; N, 20.69;
11 Found: C, 53.15; H, 7.56; Cl, 13.27; N, 20.41.

12 EXAMPLE 14

13 1-Methyl-4-(3-nitro-4-pyridyl)-pyrazole

14 Step A: Preparation of (3-Nitro-4-pyridyl)malondialdehyde

15 To dimethylformamide (22 g., 0.3 mole) is added
16 with stirring and cooling phosphorus oxychloride (9.2 g.,
17 0.06 mole). After 15 minutes, 3-nitro-4-picoline hydro-
18 chloride (3.5 g., 0.02 mole) is added. The reaction mix-
19 ture then is heated at 70° C. for 6 hours and left at room
20 temperature overnight. The reaction mixture is poured onto
21 70 g. of ice and brought to alkaline pH with concentrated
22 ammonium hydroxide. After stirring for 10 minutes, the reac-
23 tion mixture is heated on the steam bath for another 10
24 minutes, cooled with an ice bath and the pH adjusted to 4
25 with concentrated hydrochloric acid. The volume is reduced
26 on the flash evaporator to half the original volume and left
27 in the refrigerator for several hours. The salt is filtered
28 off, washed with a small amount of water and the filtrate
29 evaporated to half its volume and left in the refrigerator
30 overnight. The crystals are filtered, washed with ice cold
31 methanol and air dried yielding 0.85 g. of product, m.p.
32 178° C.

994338

1 Analysis calculated for $C_8H_6N_2O_4 \cdot H_2O$:

2 N, 13.20;

3 Found: N, 13.15.

4 Step B: Preparation of 1-methyl-4-(3-nitro-4-pyridyl)-pyra-
5 zole

6 The (3-nitro-4-pyridyl)malondialdehyde (5 g., 26
7 mmoles) and methylhydrazine (1.2 g.) are reacted in 25 ml.
8 2N hydrochloric acid. Heating on the steam bath is continued
9 for two hours, the reaction mixture then is made basic with
10 sodium hydroxide and extracted with ether. The ethereal
11 phase is dried over magnesium sulfate and taken to dryness,
12 the residue dissolved in boiling petroleum ether, the insolu-
13 bles decanted and the petroleum fraction taken to dryness
14 yielding 1 g. of 1-methyl-4-(3-nitro-4-pyridyl)-pyrazole,
15 m.p. 68-70° C.

16 Analysis calculated for $C_9H_8N_4O_2$:

17 C, 52.94; H, 3.95; N, 27.44;

18 Found: C, 52.57; H, 3.84; N, 27.12.

19 EXAMPLE 15

20 1-Methyl-4-(3-amino-4-pyridyl)-pyrazole

21 1-Methyl-4-(3-nitro-4-pyridyl)-pyrazole, (Exam-
22 ple 14) (3 g., 14.5 mmoles) is dissolved in concentrated
23 hydrochloric acid (12 ml.). Hydrated stannous chloride
24 (21 g., 0.1 mole) in 12 ml. concentrated hydrochloric acid
25 is added and the reaction progresses readily. The solid
26 material is separated by filtration and dried yielding 1-
27 methyl-4-(3-amino-4-pyridyl)-pyrazole, m.p. 134-137° C.

994338

1 Analysis calculated for $C_9H_{10}N_4$:
2 C, 62.05; H, 5.79; N, 32.16;
3 Found: C, 62.14; H, 5.95; N, 31.86.

4 EXAMPLE 16

5 1-Methyl-4-(3-acetamido-4-pyridyl)-pyrazole hydrogen maleate
6 1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example
7 15) (100 mg., 0.5 mmole) is added to 10 ml. pyridine and 5
8 ml. acetic anhydride. The solution is heated on the steam
9 bath overnight, the reaction mixture then flashed down to
10 dryness and the resulting oil dissolved in 5 ml. isopro-
11 panol. Maleic acid (116 mg., 1 mmole) in 5 ml. isopropanol
12 is added and the solution slowly concentrated until there
13 is an indication of crystallization. The solution is
14 placed in the refrigerator for several hours, the solid
15 maleate salt is filtered off, washed with cold isopropanol
16 and air dried, yielding 90 mg. of 1-methyl-4-(3-acetamido-
17 4-pyridyl)-pyrazole hydrogen maleate, m.p. 125-126° C.

18 NMR: ppm: 8.97 s(1H, pyrazole proton); 8.68 s(1H,
19 pyrazole proton); 6.35 s(2H, maleate pro-
20 tons); 3.99 s(3H, N-CH₃); 2.15 s(3H, COCH₃).

21 Note: The NMR's reported for some of the compounds
22 were run in DMSO except where otherwise noted.

994338

EXAMPLE 17

1-Methyl-4-(3-dimethylamino-4-pyridyl)-pyrazole
hydrogen maleate monohydrate

1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example 15) (100 mg., 0.5 mmole) is added to 1 ml. of formaldehyde (37% v/v) and 2 ml. formic acid. The materials are refluxed on the steam bath overnight when analysis by TLC (thin layer chromatography) will show the reaction is complete. The resulting solution is made basic with sodium hydroxide and extracted with ethyl acetate. The oily residue, obtained after evaporation of the solvent, is treated with 87 mg. maleic acid in 5 ml. isopropanol. As no precipitate is formed, the isopropanol solution is evaporated to dryness and the oil slowly crystallizes yielding 120 mg. of 1-methyl-4-(3-dimethylamino-4-pyridyl)-pyrazole hydrogen maleate monohydrate, m.p. 139° C.

Analysis calculated for $C_{11}H_{14}N_4 \cdot C_4H_4O_4 \cdot H_2O$:

C, 53.56; N, 5.99;

Found: C, 53.47; N, 5.60.

EXAMPLE 18

1-Methyl-4-(3-phenyl-4-pyridyl)-pyrazole

1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example 15) (150 mg., 0.73 mmole) is treated with isoamyl nitrite (0.5 ml.) in 10 ml. benzene and the solution refluxed for 2 hours. The reaction mixture is pumped to dryness, water is added and the mixture then made basic with sodium hydroxide and extracted with ethyl acetate. A TLC analysis shows the residue contains two components which are separated by preparative TLC. The 1-methyl-4-(3-phenyl-4-pyridyl)-pyrazole is obtained as an oil, yield 52 mg. The second component is 1-methyl-4-(4-pyridyl)-pyrazole.

994338

1 NMR: ppm: 7.40 s(5H, phenyl proton); 7.35 s(1H, pyrazole
2 proton); 6.99 s(1H, pyrazole proton); 3.77
3 s(3H, N-CH₃).

4 Mass Spectrum: M⁺ 235.

5 EXAMPLE 19

6 1-Methyl-4-(3-hydroxy-4-pyridyl)-pyrazole

7 1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example
8 15) (150 mg., 0.73 mmole) is dissolved in 5 ml. of water
9 containing 250 mg. concentrated sulfuric acid and the solu-
10 tion stirred in an ice bath while sodium nitrite (83 mg.) in
11 1 ml. of ice cold water is added dropwise. The resulting
12 solution containing the diazonium salt is stirred in the ice
13 bath for an additional hour. Water (3.2 ml.) and concentra-
14 ted sulfuric acid (0.8 ml.) are placed in a separate 50 ml.
15 flask. The solution is warmed on the steam bath and the
16 diazonium salt solution added with a pipet. After heating
17 for 5 minutes, TLC shows that the reaction is complete.
18 The reaction mixture is adjusted to pH 7 and the solution
19 placed in the refrigerator overnight. The crystals are
20 filtered and air dried yielding 1-methyl-4-(3-hydroxy-4-
21 pyridyl)-pyrazole, (90 mg.), m.p. 164-165° C.

22 NMR: ppm: 8.34 s(1H, pyrazole proton); 8.21 s(1H,
23 pyrazole proton); 3.98 s(3H, N-CH₃).

24 Mass Spectrum: M⁺ 175.

25 EXAMPLE 20

26 1-Methyl-4-(3-Chloro-4-pyridyl)-pyrazole
27 hydrogen maleate hemihydrate

28 1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example
29 15) (125 mg., 0.71 mmole) is dissolved in 6 ml. of water
30 and 4 ml. of 1N hydrochloric acid. The solution is stirred
31 and kept cooled in an ice bath as 80 mg. sodium nitrite
32 dissolved in 1 ml. water is added. The reaction is stirred

994338

1 in the cold for one hour. The diazonium salt is pipetted
2 onto cuprous chloride (200 mg.) in concentrated hydrochloric
3 acid (2 ml.) while maintaining the temperature at about 75°
4 C. The resulting mixture is heated on the steam bath for an
5 hour, the solution then made basic, the copper hydroxide
6 filtered off and the solution extracted with ethyl acetate.
7 The ethyl acetate extract is concentrated under vacuum and
8 the product pumped dry under high vacuum. The maleate salt
9 is prepared in the usual manner (Example 16) yielding 250
10 mg. of 1-methyl-4-(3-chloro-4-pyridyl)-pyrazole hydrogen
11 maleate hemihydrate, m.p. 139-141° C.

12 Analysis calculated for $C_9H_8ClN_3 \cdot C_4H_4O_4 \cdot 1/2 H_2O$:

13 C, 48.99; H, 4.11; N, 13.18; Cl, 11.12;

14 Found: C, 49.06; H, 4.29; N, 12.68; Cl, 10.87.

15 EXAMPLE 21

16 1-Methyl-4-(3-cyano-4-pyridyl)-pyrazole hemihydrate

17 1-Methyl-4-(3-amino-4-pyridyl)-pyrazole (Example
18 15) (154 mg., 1 mmole) is dissolved in 5 ml. of 1N hydro-
19 chloric acid and the solution stirred in an ice bath as 80
20 mg. of sodium nitrite dissolved in 1 ml. water is added
21 dropwise. The diazonium solution is then stirred in the cold
22 for an additional hour. The solution is neutralized with
23 sodium carbonate and the neutral diazonium salt added to a
24 hot solution of potassium cuprous cyanide prepared by dis-
25 solving cuprous cyanide in potassium cyanide. The reaction
26 mixture then is heated one hour on the steam bath, cooled
27 and extracted with ethyl acetate. After drying over mag-
28 nesium sulfate and removing the solvent under vacuum, there
29 is obtained 150 mg. of 1-methyl-4-(3-cyano-4-pyridyl)-pyra-
30 zole hemihydrate, m.p. 148-151° C.

994338

Analysis calculated for $C_{10}H_8N_4 \cdot 1/2 H_2O$:

C, 62.16; H, 4.69; N, 29.00;

Found: C, 61.79; H, 4.63; N, 28.71.

EXAMPLE 22

1-(2,2,2-Trifluoroethyl)-4-(4-pyridyl)-pyrazole

A mixture of 4-pyridylmalondialdehyde (3.53 g., 23.6 mmole), 70% 2,2,2-trifluoroethylhydrazine (3.86 g., 23.6 mmole) and alcohol (50 ml.) is heated under reflux for 3 hours, and then evaporated to dryness. The residual solid is recrystallized from di-isopropyl ether to afford 2.75 g. (60%) of product, m.p. 109-111° C.

Analysis calculated for $C_{10}H_8F_3N_3$:

C, 52.87; H, 3.55; F, 25.09; N, 18.49;

Found: C, 52.95; H, 3.56; F, 25.31; N, 18.40.

EXAMPLE 23

1-(2-Hydroxyethyl)-4-(4-pyridyl)-pyrazole

A mixture of 4-pyridylmalondialdehyde (2.98 g., 20 mmole), 2-hydroxyethylhydrazine (1.52 g., 20 mmole) and 1N hydrochloric acid (40 ml.) is heated briefly until complete solution is obtained, and then allowed to stand at room temperature for 2 hours. After the reaction is made basic with ammonium hydroxide, the product is isolated by continuous extraction with methylene chloride and purified by recrystallization from benzene yielding 1.1 g. (29%) of product, m.p. 114-116° C.

Analysis calculated for $C_{10}H_{11}N_3O$:

C, 63.48; H, 5.86; N, 22.21;

Found: C, 63.58; H, 5.94; N, 22.31.

EXAMPLE 24

1-(2-Methoxyethyl)-4-(4-pyridyl)-pyrazole hydrochloride

A mixture of 4-pyridylmalondialdehyde (7.5 g., 50

994338

1 mmole), methoxyethylhydrazine (5.85 g., 65 mmole), acetic
2 acid (6.5 ml.) and benzene (200 ml.) is stirred at reflux
3 under a Dean-Stark trap for 4-1/2 hours and then evapora-
4 ted in a rotary evaporator. The residual oil is treated
5 with dry ether and a slight excess of ethanolic hydrogen
6 chloride is added to precipitate the hydrochloride of the
7 product. This somewhat hygroscopic solid is dissolved in
8 isopropanol and carefully reprecipitated by adding dry
9 ether. The salt is dried and stored over calcium chloride
10 in a vacuum desiccator, yielding 7.3 g. (61%) of product,
11 m.p. 127-129° C.

12 Analysis calculated for $C_{11}H_{13}N_3O \cdot HCl$:

13 C, 55.12; H, 5.88; N, 17.53; Cl, 14.79;

14 Found: C, 54.41; H, 6.17; N, 17.58; Cl, 14.96.

15 EXAMPLE 25

16 1-(2-Dimethylaminoethyl)-4-(4-pyridyl)-pyrazole
17 dihydrochloride

18 A mixture of 4-pyridylmalondialdehyde (1.49 g.,
19 10 mmole), 2-dimethylaminoethylhydrazine (1.34 g., 13
20 mmole), acetic acid (1.5 ml.) and benzene (40 ml.) is
21 heated at reflux under a Dean-Stark trap overnight. The sol-
22 vent is evaporated under vacuum and the oily residue is made
23 basic with 10N sodium hydroxide (3 ml.) and partitioned be-
24 tween ethyl acetate and water. The ethyl acetate extract is
25 dried over magnesium sulfate and evaporated to afford a pale
26 yellow oil. Dissolution of the oil in isopropanol and acidi-
27 fication with hydrogen chloride in ethanol gives 2 g. of
28 the hydrochloride of the product as a hygroscopic solid
29 which, after recrystallization from absolute ethanol affords
30 1.25 g. of pure material, m.p. 253-255° C.

994338

1 Analysis calculated for $C_{12}H_{16}N_4 \cdot 2HCl$:

2 C, 49.83; H, 6.27; Cl, 24.52; N, 19.37;

3 Found: C, 49.95; H, 6.40; Cl, 24.29; N, 19.22.

4 The di(hydrogen maleate)salt of 1-(2-dimethyl-
5 aminoethyl)-4-(4-pyridyl)-pyrazole is prepared by the pro-
6 cess described in Example 16, employing an excess of maleic
7 acid, giving product melting at 137-138° C. (dec.).

8 Analysis calculated for $C_{12}H_{16}N_4 \cdot 2C_4H_4O_4$:

9 C, 53.57; H, 5.39; N, 12.49;

10 Found: C, 53.65; H, 5.45; N, 12.32.

11 EXAMPLE 26

12 1-(4-Pyridylmethyl)-4-(4-pyridyl)-pyrazole

13 A mixture of 4-picolyldiazine dihydrochloride
14 (1.75 g., 8.92 mmole), 4-pyridylmalondialdehyde (1.33 g.,
15 8.92 mmole) and water (20 ml.) is heated for a few minutes
16 on a steam bath until the aldehyde dissolves, and the solu-
17 tion is allowed to stand at ambient temperature for 2 hours,
18 before being made basic with ammonium hydroxide. The solid
19 is collected, washed with water and dried to provide 1.35 g.
20 (64%) of product, m.p. 129-134° C. Further recrystalliza-
21 tion from di-isopropyl ether raises the melting point to
22 133-135° C.

23 Analysis calculated for $C_{14}H_{12}N_4$:

24 C, 71.17; H, 5.12; N, 23.71;

25 Found: C, 71.35; H, 5.11; N, 23.83.

26 EXAMPLE 27

27 1-[2-(4-Pyridyl)-ethyl]-4-(4-pyridyl)-pyrazole
28 dihydrochloride dihydrate

29 A mixture of 4-pyridylmalondialdehyde (5.96 g.,
30 40 mmole), 4-(2-hydrazinoethyl)-pyridine (7.1 g., 52 mmole),
31 acetic acid (5.2 ml.) and benzene (160 ml.) is stirred at

994338

1 reflux under a Dean-Stark trap for 4-1/2 hours. The reac-
2 tion mixture is evaporated and the residue is dissolved in
3 isopropanol. Addition of a slight excess (>2 equivalents)
4 of ethanolic hydrogen chloride yields the crude hydrochlor-
5 ide as a precipitate. The solid is collected and recrystal-
6 lized from ethanol to afford 6.2 g. (45%) of product, m.p.
7 252-254° C.

8 Analysis calculated for $C_{15}H_{14}N_4 \cdot 2HCl \cdot 2H_2O$:
9 C, 50.15; H, 5.60; Cl, 19.73; N, 15.59;
10 Found: C, 50.05; H, 6.29; Cl, 19.52; N, 15.53.

11 EXAMPLE 28

12 Ethyl [4-(4-pyridyl)-1-pyrazolyl]-acetate

13 By replacing t-butylhydrazine hydrochloride in
14 Example 2 by an equivalent quantity of ethyl hydrazinoace-
15 tate hydrochloride and following substantially the same
16 procedure, there is obtained ethyl [4-(4-pyridyl)-1-pyra-
17 zolyl]-acetate in 88% yield. The compound crystallizes
18 from water in colorless plates, m.p. 96.5-97.5° C.

19 Analysis calculated for $C_{12}H_{13}N_3O_2$:
20 C, 62.32; H, 5.66; N, 18.17;
21 Found: C, 61.98; H, 5.84; N, 17.81.

22 EXAMPLE 29

23 [4-(4-Pyridyl)-1-pyrazolyl]-N,N-dimethyl acetamide
24 hydrochloride

25 Ethyl [4-(4-pyridyl)-1-pyrazolyl]-acetate (Example
26 28) (2.31 g., 10 mmoles) is dissolved in ethanol (10 ml.)
27 saturated with dimethylamine and left at ambient temperature
28 for three days. The solvent then is removed under vacuum,
29 leaving an oil that slowly crystallizes. The yield is
30 essentially quantitative, with a recovery of 2.25 g. of [4-
31 (4-pyridyl)-1-pyrazolyl]-N,N-dimethyl acetamide hydrochlor-
32 ide, m.p. 286-288° C.

Analysis calculated for $C_{12}H_{14}N_4O \cdot HCl$:

C, 54.03; H, 5.67; N, 21.01; Cl, 13.29;

Found: C, 54.40; H, 6.36; N, 20.87; Cl, 13.26.

EXAMPLE 30

1-Ethylcarbamoyl-4-(4-pyridyl)-pyrazole

A mixture of 4-(4-pyridyl)-pyrazole (600 mg., 4 mmole), ethyl isocyanate (10 ml.) and triethylamine (1 ml.) is heated under reflux for 3 hours and then evaporated to dryness. The residue is recrystallized from ethyl acetate to give 400 mg., (46%) of product, m.p. 159-163° C.

Analysis calculated for $C_{11}H_{12}N_4O$:

C, 61.10; H, 5.59; N, 25.91;

Found: C, 60.87; H, 5.68; N, 26.05.

EXAMPLE 31

1-Dimethylcarbamoyl-4-(4-pyridyl)-pyrazole

A mixture of 4-pyridylmalondialdehyde (3.0 g., 20 mmole), 4,4-dimethylsemicarbazide (2.06 g., 20 mmole) and 2N hydrochloric acid (20 ml.) is warmed briefly to effect solution, and then set aside at ambient temperature overnight. Addition of 2N sodium hydroxide solution (21 ml.) precipitates the crude product, 3.4 g., m.p. 123-127° C. Recrystallization of the solid from water affords 2.3 g. (54%) of 1-dimethylcarbamoyl-4-(4-pyridyl)-pyrazole, m.p. 130-131° C.

Analysis calculated for $C_{11}H_{12}N_4O$:

C, 61.10; H, 5.59; N, 25.91;

Found: C, 60.66; H, 5.89; N, 25.83.

By replacing the 4,4-dimethylsemicarbazide in Example 31 by an equivalent quantity of 4,4-di-isopropylsemicarbazide and following substantially the same procedure there is obtained 1-di-isopropylcarbamoyl-4-(4-pyridyl)-pyrazole.

EXAMPLE 32

1-(4-Methylpiperazinocarbonyl)-4-(4-pyridyl)-pyrazole

994338

1 4-Pyridylmalondialdehyde (3.0 g., 20 mmole) is dis-
2 solved in 1N hydrochloric acid (40 ml.) and 4-methylpiperazine-
3 l-carboxylic acid hydrazide (3.16 g., 20 mmole) is added. The
4 mixture is heated briefly on a steam bath to get a clear solu-
5 tion and allowed to stand at room temperature for 3 hours and
6 then neutralized with 2N sodium hydroxide (20 ml.). The solid
7 is collected and recrystallized from hot water (ca. 60 ml.)
8 giving 3.8 g. (69%) of product in colorless needles, m.p.
9 139-140° C.

10 Analysis calculated for $C_{14}H_{17}N_5O$:
11 C, 61.97; H, 6.31; N, 25.81;
12 Found: C, 61.71; H, 6.44; N, 26.25.

13 EXAMPLE 33

14 1-Piperidinocarbonyl-4-(4-pyridyl)-pyrazole

15 Replacement of 4-methylpiperazine-1-carboxylic acid
16 hydrazide in Example 32 with an equivalent quantity of piperi-
17 dine-1-carboxylic acid hydrazide and following the procedure
18 there described, there is obtained 1-piperidinocarbonyl-4-(4-
19 pyridyl)-pyrazine in 53% yield, m.p. 157-161° C. after re-
20 crystallization from water.

21 Analysis calculated for $C_{14}H_{16}N_4O$:
22 C, 65.60; H, 6.29; N, 21.86;
23 Found: C, 65.73; H, 6.51; N, 21.85.

24 EXAMPLE 34

25 1-Phenyl-4-(4-pyridyl)-pyrazole

26 A mixture of 4-pyridylmalondialdehyde (1.49 g.,
27 10 mmole), phenylhydrazine hydrochloride (1.44 g., 10 mmole),
28 1N hydrochloric acid (10 ml.) and water (10 ml.) is heated
29 briefly on a steam bath until solution occurs and is allowed
30 to stand at ambient temperature for 3 hours before addition
31 of 2N sodium hydroxide (10.5 ml.). The solid is collected,
32 washed with water and dried yielding 1.85 g. (83%) of pro-
33 duct, m.p. 127-130° C. On recrystallization from a mixture

994338

1 of benzene and petroleum ether, the melting point is raised
2 to 130-132° C.

3 Analysis calculated for $C_{14}H_{11}N_3$:
4 C, 76.00; H, 5.01; N, 18.99;
5 Found: C, 75.71; H, 5.21; N, 19.47.

6 EXAMPLE 35

7 1-Amidino-4-(4-pyridyl)-pyrazole

8 By replacing methylhydrazine in Example 1 with an
9 equivalent quantity of aminoguanidine bicarbonate and fol-
10 lowing substantially the same procedure, there is obtained
11 1-amidino-4-(4-pyridyl)-pyrazole in 59% yield, m.p. 143-145°
12 C. after recrystallization from water. The compound also
13 exists in a crystalline form of m.p. 158-160° C.

14 Analysis calculated for $C_9H_9N_5$:
15 C, 57.74; H, 4.84; N, 37.41;
16 Found: C, 57.60; H, 4.78; N, 37.74.

17 The base forms a salt with isethionic acid, m.p.
18 173-173.5° C. following recrystallization from aqueous
19 methanol.

20 Analysis calculated for $C_9H_9N_5 \cdot C_2H_6O_4S$:
21 C, 42.17; H, 4.83; N, 22.35; S, 10.23;
22 Found: C, 42.24; H, 4.73; N, 22.22; S, 10.18.

23 EXAMPLE 36

24 1-Methylamidino-4-(4-pyridyl)-pyrazole

25 By replacing phenylhydrazine hydrochloride in
26 Example 34 with an equivalent quantity of 1-amino-4-methyl-
27 guanidine hydriodide and following substantially the same
28 procedure, there is obtained 1-methylamidino-4-(4-pyridyl)-
29 pyrazole in 62% yield, m.p. 139-141° C. after recrystalli-
30 zation from water.

994338

1 Analysis calculated for $C_{10}H_{11}N_5$:
 2 C, 59.69; H, 5.51; N, 34.80;
 3 Found: C, 59.38; H, 5.73; N, 35.07.

EXAMPLE 37

5 1-(2-Imidazolin-2-yl)-4-(4-pyridyl)-pyrazole

6 Step A: Preparation of 2-Hydrazino-2-imidazoline hydriodide
 7 2-Methylthio-4,5-dihydroimidazole hydriodide (24.4
 8 g., 0.1 mole) and hydrazine (3.2 g., 0.1 mole) are refluxed
 9 in 50 ml. absolute ethanol for a period of two hours. A
 10 strong odor of methanethiol will be detected. The reaction
 11 mixture is left at ambient temperature overnight. Ether
 12 (300 ml.) then is added to ensure complete precipitation of
 13 the product which is filtered and air dried to yield 22.2 g.
 14 (98%) of product, m.p. 123-128° C.

15 Step B: Preparation of 1-(2-Imidazolin-2-yl)-4-(4-pyridyl)-
 16 pyrazole·1.5 H₂O

17 4-Pyridylmalondialdehyde (1.5 g., 10 mmoles) and
 18 the hydrazine derivative obtained in Step A (2.3 g., 10
 19 mmoles) are heated in 1N hydrochloric acid (10 ml.) for one
 20 hour. The resulting solution is made basic and the solid
 21 removed by filtration, washed with water and air dried
 22 yielding 1.4 g. (66%) of product, m.p. 135-138° C.

23 Analysis calculated for $C_{11}H_{11}N_5 \cdot 1.5 H_2O$:
 24 C, 54.81; H, 5.92;
 25 Found: C, 54.99; H, 5.87.

EXAMPLE 38

27 4-(4-Pyridyl)-1-[2-(3,4-dihydro-1,3-thiazolyl)]-pyrazole
 28 and
 29 4-(4-Pyridyl)-1-[2-(5,6-dihydro-4(H)-1,3-thiazinyl)]-pyrazole

30 Step A-1: Preparation of 2-Hydrazino-4,5-dihydro-1,3-thia-
 31 zole hydriodide

32 2-Methylthio-4,5-dihydro-1,3-thiazole hydriodide
 33 (6 g., 25 mmoles) and 85% hydrazine hydrate (1.5 g., 25

994338

1 mmoles) are refluxed in methanol (25 ml.) for two hours,
2 then cooled and ether (150 ml.) added. The solid is fil-
3 tered and air dried giving a 52% yield of product, m.p.
4 148-150° C.

5 Analysis calculated for $C_3H_7N_3S \cdot HI$:

6 C, 14.70; H, 3.29; N, 17.15; S, 13.08; I, 51.78;
7 Found: C, 15.02; H, 3.45; N, 17.15; S, 13.66; I, 51.51.

8 Step A-2: Preparation of 2-Hydrazino-5,6-dihydro-4(h)-1,3-
9 thiazine hydriodide

10 In a similar fashion, from 2-methylthio-5,6-dihy-
11 dro-4(H)-1,3-thiazine hydriodide (6 g., 20 mmoles) and 85%
12 hydrazine hydrate (1.2 g., 20 mmoles), 2-hydrazino-5,6-di-
13 hydro-4(H)-1,3-thiazine hydriodide is obtained in a yield
14 of 85% (5 g.), m.p. 158-159° C.

15 NMR: ppm: 10.5 (1H, NH proton); 6.2 (1H, NH proton);
16 3.5 t(2H, CH_2 α to N, $J = 7$ Hz); 3.2 t(2H,
17 CH_2 α to S, $J = 7$ Hz); 2.10 quintet(2H,
18 middle CH_2 , $J = 7$ Hz).

19 Step B-1: Preparation of 4-(4-Pyridyl)-1-[2-(3,4-dihydro-
20 1,3-thiazolyl)]-pyrazole-hemihydrate

21 4-Pyridylmalondialdehyde (1.5 g., 10 mmoles) and
22 the hydrazine from Step A-1 (2.5 g., 10 mmoles) are heated
23 on the steam bath in 10 ml. of water. The heating is stopped
24 when the malondialdehyde is completely dissolved, the reac-
25 tion mixture cooled and the solution made basic by addition
26 of sodium hydroxide. The solid is filtered and air dried to
27 give 1.5 g. (65%) of product, m.p. 152-153° C.

28 Analysis calculated for $C_{11}H_{10}N_4S \cdot 1/2 H_2O$:

29 C, 55.21; H, 4.63; N, 23.41;

30 Found: C, 55.98; H, 5.08; N, 23.57.

994338

1 Step B-2: Preparation of 4-(4-Pyridyl)-1-[2-(5,6-dihydro-
 2 4(H)-1,3-thiazinyl)]-pyrazole

3 In a similar fashion, from the hydrazine of Step
 4 A-2, (2.5 g., 10 mmoles) and 4-pyridylmalondialdehyde (1.5
 5 g., 10 mmoles), 4-(4-pyridyl)-1-[2-(5,6-dihydro-4(H)-1,3-
 6 thiazinyl)]-pyrazole is obtained in 70% yield, m.p. 162-
 7 163° C.

8 NMR: ppm: 9.18 s(1H, pyrazole proton); 8.78 d(1H, α
 9 proton, $J = 6$ Hz); 8.52 s(1H, pyrazole pro-
 10 ton); 7.85 d(1H, β proton, $J = 6$ Hz); 3.95
 11 and 3.20 t(2H, CH_2 α to N and S, $J = 7$ Hz);
 12 1.95 q(2H, middle CH_2 , $J = 7$ Hz).

13 EXAMPLE 39

14 3,4-Di(4-pyridyl)-pyrazole·dihydrochloride monohydrate

15 To 4-pyridylmethyl 4-pyridyl ketone (3.88 g., 20
 16 mmoles) in benzene (20 ml.) is added sodium methoxide (1 g.)
 17 and ethyl formate (1.4 g.). The reaction mixture is heated
 18 at reflux for one hour and then cooled to ambient tempera-
 19 ture. The sodium salt of the keto aldehyde formed is fil-
 20 tered off, washed with benzene and ether and reacted with
 21 hydrazine hydrate (1.2 g.), glacial acetic acid (1.2 g.)
 22 and water (40 ml.). The mixture is heated on the steam
 23 bath for one hour, the reaction mixture then made basic
 24 with sodium hydroxide and extracted with ethyl acetate. The
 25 solvent is dried over magnesium sulfate and concentrated
 26 under vacuum. The residue is recrystallized from chloro-
 27 form-petroleum ether, yielding 1 g. of product, m.p. 128-
 28 130° C. The hydrochloride monohydrate is prepared in the
 29 usual manner, m.p. 190-192° C. (dec.).

30 Analysis calculated for $\text{C}_{13}\text{H}_{10}\text{N}_4 \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$:

31 C, 49.54; H, 5.12; N, 17.77; Cl, 22.50;

32 Found: C, 50.03; H, 4.84; N, 17.89; Cl, 22.30.

994338

EXAMPLE 40

1-[2-(3,4,5,6-Tetrahydropyrimidinyl)]-4-(4-pyridyl)-pyrazole trihydrochloride, hemihydrate

Step A: Preparation of 2-Hydrazino-3,4,5,6-tetrahydropyrimidine hydriodide

2-Methylmercapto-3,4,5,6-tetrahydropyrimidine hydriodide (25.8 g., .1 mole) and hydrazine (3.2 g., 0.1 mole) are refluxed in methanol (50 ml.) for two hours, (a strong odor of methanethiol is detected) and then left at ambient temperature overnight. Ether (300 ml.) is added to ensure complete precipitation of the product in the form of its hydriodide salt which is filtered and air dried yielding 22.8 g. (98%) of product, m.p. 160° C.

Analysis calculated for $C_4H_{11}N_4I$:

C, 19.85; H, 4.58; N, 23.15; I, 52.43;

Found: C, 19.95; H, 4.73; N, 23.30; I, 52.63.

Step B: Preparation of 1-[2-(3,4,5,6-Tetrahydropyrimidinyl)]-4-(4-pyridyl)-pyrazole trihydrochloride hemihydrate

4-Pyridylmalondialdehyde (1.5 g., 10 mmoles) and the hydrazine derivative of Step A (2.5 g., 10 mmoles) are heated in 1N hydrochloric acid (10 ml.) for one hour. The resulting solution is made basic with ammonium hydroxide and the solid is filtered, washed with water and air dried, yielding 1.5 g. (65%) of product, m.p. 296-298° C. The hydrochloride salt is prepared by crystallizing from hydrochloric acid, m.p. 301-304° C.

Analysis calculated for $C_{12}H_{13}N_5 \cdot 3HCl \cdot 1/2 H_2O$:

C, 41.70; H, 4.95; N, 20.26;

Found: C, 41.34; H, 4.65; N, 20.36.

EXAMPLE 41

1,4-Di-(4-pyridyl)-pyrazole

A mixture of 4-pyridylmalondialdehyde (1.49 g.,

994338

1 10 mmole), 4-hydrazinopyridine hydrochloride (1.5 g., 10.3
2 mmole) and 85% phosphoric acid (25 ml.) is heated on a steam
3 bath for 5 hours, then poured into ice water and made basic
4 with ammonium hydroxide to precipitate the crude product,
5 which on recrystallization from water (ca. 90 ml.) separates
6 in long colorless needles, m.p. 146-147° C., 1.9 g. (86%).

7 Analysis calculated for $C_{13}H_{10}N_4$:

8 C, 70.25; H, 4.54; N, 25.21;

9 Found: C, 70.76; H, 4.63; N, 24.70.

10 EXAMPLE 42

11 1-(3-Pyridyl)-4-(4-pyridyl)-pyrazole

12 By replacing in the reaction described in Example
13 41 the 4-hydrazinopyridine hydrochloride with an equivalent
14 amount of 3-hydrazinopyridine oxalate, there is obtained
15 1-(3-pyridyl)-4-(4-pyridyl)-pyrazole. After making the
16 reaction mixture basic the product is isolated by extraction
17 with ethyl acetate. Following recrystallization from ben-
18 zene and treatment with charcoal there is obtained a 55%
19 yield of product, m.p. 153-155° C.

20 Analysis calculated for $C_{13}H_{10}N_4$:

21 C, 70.25; H, 4.54; N, 25.21;

22 Found: C, 69.96; H, 4.59; N, 25.44.

23 EXAMPLE 43

24 1-(2-Pyridyl)-4-(4-pyridyl)-pyrazole

25 By replacing 4-hydrazinopyridine hydrochloride em-
26 ployed in Example 41 with an equivalent quantity of 2-hydra-
27 zinopyridine hydrochloride there is obtained a 45% yield of
28 1-(2-pyridyl)-4-(4-pyridyl)-pyrazole which after recrystal-
29 lization from di-isopropyl ether, melts at 109-111° C.

994338

1 Analysis calculated for $C_{13}H_{10}N_4$:
2 C, 70.25; H, 4.54; N, 25.21;
3 Found: C, 70.23; H, 4.46; N, 24.90.

4 EXAMPLE 44

5 1-Amidino-5-amino-4-(4-pyridyl)-pyrazole
6 To 2-formyl-2-(4-pyridyl)-acetonitrile (7.3 g.,
7 50 mmole) suspended in 1N hydrochloric acid (100 ml.) is
8 added in small portions aminoguanidine bicarbonate (6.8 g.,
9 50 mmole) and the mixture is heated on a steam bath for one
10 hour. After a further 3 hours at room temperature the mix-
11 ture is filtered and the filtrate made basic with 2N sodium
12 hydroxide solution to give 4.0 g., (40%) of crude product,
13 m.p. 179-181° C. Recrystallization of the crude product
14 from ethyl acetate gives pure 1-amidino-5-amino-4-(4-pyri-
15 dyl)-pyrazole, m.p. 185-186° C.

16 Analysis calculated for $C_9H_{10}N_6$:
17 C, 53.45; H, 4.98; N, 41.56;
18 Found: C, 53.26; H, 5.08; N, 41.81.

19 EXAMPLE 45

20 1-N-Methylthiocarbamoyl-4-(4-pyridyl)-pyrazole
21 A solution of 4-methylthiosemicarbazide (1.31 g.,
22 12.5 mmole) in water (13 ml.) is added to a warm solution
23 of 4-pyridylmalondialdehyde (1.49 g., 10 mmole) in methanol
24 (150 ml.) containing a few drops of acetic acid. The mix-
25 ture is heated under reflux for 6 hours, cooled and the solid
26 collected yielding 924 mg. (42%) of product, m.p. 170-172°
27 C. Recrystallization from aqueous methanol provides product
28 in the form of colorless needles, m.p. 172-173.5° C.

29 Analysis calculated for $C_{10}H_{10}N_4S$:
30 C, 55.03; H, 4.62; N, 25.67; S, 14.69;
31 Found: C, 55.23; H, 4.63; N, 25.40; S, 14.72.

994338

EXAMPLE 46

1 1-Propargyl-4-(4-pyridyl)-pyrazole hydrochloride monohydrate
2
3 4-(4-Pyridyl)-pyrazole (2.90 g., 20 mmole) is
4 added to a solution of sodium (460 mg., 20 mmole) in dry
5 ethanol (30 ml.), and then propargyl bromide (2.38 g., 20
6 mmole) is added. The mixture is stirred at room temperature
7 for 48 hours and evaporated in a rotary evaporator. The
8 residue is partitioned between ether and dilute sodium hy-
9 droxide solution thereby removing unreacted pyridyl-pyrazole
10 from the ether solution. Evaporation of the dried (over
11 magnesium sulfate) ethereal solution affords 1.4 g. of oil
12 which is dissolved in isopropanol and a slight excess of
13 ethanolic hydrogen chloride is added to precipitate the
14 hydrochloride of the product. The crude salt on recrystal-
15 lization from a mixture of methanol and isopropanol affords
16 1.4 g. (29.5%) of product, m.p. 203-205° C.

17 Analysis calculated for $C_{11}H_9N_3 \cdot HCl \cdot H_2O$:

18 C, 55.58; H, 5.08; Cl, 14.91; N, 17.67;

19 Found: C, 55.71; H, 5.12; Cl, 14.65; N, 17.60.

EXAMPLE 47

21 5-Amino-1-ethoxycarbonylmethyl-4-(4-pyridyl)-pyrazole
22 hydrochloride

23 A mixture of 2-formyl-(4-pyridyl)-acetonitrile
24 (2.98 g., 20 mmole), ethylhydrazinoacetate hydrochloride
25 (4.0 g., 26 mmole), sodium acetate trihydrate (3.50 g.,
26 26 mmole), acetic acid (3.5 ml.) and benzene (80 ml.) is
27 stirred under reflux under a Dean-Stark trap for 4 hours
28 by which time 2.2 ml. of water is collected. Some unreacted
29 cyano aldehyde remains unreacted and therefore more ethyl-
30 hydrazinoacetate hydrochloride (1.0 g., 6.5 mmole) and sod-
31 ium acetate trihydrate (900 mg., 6.5 mmole) is added and the

994338

1 mixture heated for an additional 6 hours. A further 6.5
2 mmole of each of the two compounds is added and the mixture
3 is heated overnight. The benzene is evaporated under re-
4 duced pressure and the residue is extracted with boiling
5 isopropanol. Treatment of the filtrate with ethanolic hy-
6 drogen chloride precipitates the hydrochloride of the pro-
7 duct and more is obtained by addition of a little dry ether
8 providing a total yield of 2.4 g. (42%), m.p. 210-215° C.
9 (dec.). Recrystallization of the salt from absolute ethanol
10 affords pure compound, m.p. 227-229° C. (dec.).

11 Analysis calculated for $C_{12}H_{14}N_4O_2 \cdot HCl$:

12 C, 50.98; H, 5.35; Cl, 12.54; N, 19.81;

13 Found: C, 50.66; H, 5.47; Cl, 12.62; N, 19.94.

14 EXAMPLE 48

15 1-Methyl-4-(4-pyridyl)-5-(1-pyrrolyl)-pyrazole hydrochloride

16 A mixture of 1-methyl-4-(4-pyridyl)-5-amino-pyra-
17 zole (1.74 g., 10 mmole), prepared as described in Example
18 6, 2,5-dimethoxy-tetrahydrofuran (1.32 g., 10 mmole) and
19 acetic acid (10 ml.) is heated on a steam bath for 30 min-
20 utes and then under reflux in an oil bath for 30 minutes.
21 The acetic acid is distilled off under vacuum and the resi-
22 due is dissolved in isopropanol (20 ml.) and a slight ex-
23 cess of ethanolic hydrogen chloride solution is added to
24 afford 2.39 g. of the hydrochloride of the product, m.p. ca.
25 275-285° C. The solid sublimes readily above about 240° C.
26 Purification can be effected by recrystallization from 1:1
27 ethanol/isopropanol from which the compound separates in
28 glistening crystals, m.p. 285-287° C. with marked sublimation.

29 Analysis calculated for $C_{13}H_{12}N_4 \cdot HCl$:

30 C, 59.89; H, 5.03; Cl, 13.60; N, 21.49;

31 Found: C, 59.56; H, 5.22; Cl, 13.36; N, 21.71.

994338

EXAMPLE 49

1-(2-Dimethylaminoethyl)-4-(4-pyridyl)-5-amino-pyrazole
hydrochloride

A mixture of 2-formyl-2-(4-pyridyl)-acetonitrile (1.46 g., 10 mmole), 2-dimethylaminoethylhydrazine (1.34 g., 13 mmole), benzene (40 ml.) and acetic acid (1.5 ml.) is heated under reflux overnight. Evaporation of the solvent yields an oil, which is dissolved in water. The solution is made basic with 10N sodium hydroxide solution (3 ml.). Continuous extraction with methylene chloride provides the free base as an oil (1.2 g.). The oil is dissolved in isopropanol and acidified with ethanolic hydrogen chloride thereby precipitating 950 mg. of the hydrochloride of the product which, following crystallization from a mixture of methanol and ether, yields 230 mg. of product, m.p. 293-295° C. (dec.).

$\int_{D_2O}^{DSS}$ NMR: ppm: 8.70 d(2H, J = 7 Hz, α -pyridyl proton);
 8.23 s(1H, pyrazole proton); 8.16 d(2H,
 J = 7 Hz, β -pyridyl proton); 4.68
 t(2H, J = 6.5 Hz, CH₂); 3.87 t(2H,
 J = 6.5 Hz, CH₂); 3.17 s(6H, 2 x CH₃).

EXAMPLE 50

1-(1-Methyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole
dihydrochloride monohydrate

Step A: Preparation of 1-methyl-2-imidazolidinethione

N-Methylethylenediamine (37 g., 0.5 mole) in ether (80 ml.) is cooled to 10° C. in an ice bath and stirred vigorously while carbon disulfide (38 g.) in ether (30 ml.) is added dropwise. Stirring is continued for 30 minutes after addition is complete. The precipitate is removed by filtration, washed with ether and air-dried. The residue is heated

994338

1 in an open flask immersed in an oil bath at 130° C. for two
 2 hours and the resulting residue recrystallized from hexane
 3 to give 25 g. (43%) yield of product, m.p. 126-128° C.

4 By replacing the N-methylethylenediamine by an
 5 equivalent quantity of N-ethyl-, N-propyl-, N-butyl-, N-
 6 pentyl- or other desired N-alkylethylenediamine the corre-
 7 sponding 1-alkyl-2-imidazolidinethione is obtained.

8 Step B: Preparation of 1-Methyl-2-methylthio-2-imidazoline
 9 hydriodide monohydrate

10 1-Methyl-2-imidazolidinethione (17.4 g., 0.15
 11 mole) and methyl iodide (21.3 g., 0.15 mole) are refluxed
 12 in absolute ethanol (100 ml.) for a period of 2 hours. Upon
 13 cooling, the crystals that form are separated by filtration
 14 and air dried yielding 24 g. (62%) of compound, m.p. 96.5-
 15 98° C.

17 Analysis calculated for $C_5H_{10}N_2S \cdot HI \cdot H_2O$:
 17 C, 21.75; H, 4.75; N, 10.15; I, 45.96;
 18 Found: C, 22.16; H, 5.06; N, 10.41; I, 46.21.

19 Step C: Preparation of 1-Methyl-2-hydrazino-2-imidazoline
 20 hydriodide

21 1-Methyl-2-methylthio-2-imidazoline hydriodide
 22 (13 g., 0.05 mole) and hydrazine hydrate (5 g.) are reacted
 23 according to the procedure described in Example 37, Step A,
 24 to give 10.9 g. (89%) of compound, m.p. 180-182° C.

25 Analysis calculated for $C_4H_{10}N_4 \cdot HI$:
 26 C, 19.85; H, 4.58; N, 23.15; I, 52.43;
 27 Found: C, 20.12; H, 4.50; N, 22.89; I, 52.45.

28 Step D: Preparation of 1-(1-Methyl-2-imidazolin-2-yl)-4-(4-
 29 pyridyl)-pyrazole dihydrochloride monohydrate

30 1-Methyl-2-hydrazino-2-imidazoline hydriodide (2.6
 31 g., 10 mmole) and 4-pyridyl malondialdehyde (1.5 g., 10
 32 mmole) in 2% hydrochloric acid (50 ml.) are reacted accord-
 33 ing to the procedure described in Example 37, Step B, to

994338

9

1 give 1.83 g. (81%) of product, m.p. 68-70° C. The hydro-
 2 chloride, prepared in the usual manner, melts at 257-260° C.

3 Analysis calculated for $C_{12}H_{13}N_5 \cdot 2HCl \cdot 2H_2O$:

4 C, 45.29; H, 5.38; N, 22.01; Cl, 22.28;

5 Found: C, 45.24; H, 5.45; N, 22.20; Cl, 22.28

6 EXAMPLE 51

7 1-(1-Ethyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole
 8 hydrochloride

9 Step A: Preparation of 1-Ethyl-2-methylthio-2-imidazoline
 10 hydriodide

11 1-Ethyl-2-imidazolidinethione (9 g., 0.07 mole)
 12 and methyl iodide (10 g., 0.07 mole) are refluxed in 100 ml.
 13 absolute ethanol for a period of 2 hours. Upon cooling the
 14 crystals that form are separated by filtration and air dried
 15 yielding 16.8 g. (88%) of 1-ethyl-2-methylthio-2-imidazol-
 16 ine hydriodide, m.p. 130.5-132° C.

17 Analysis calculated for $C_6H_{12}N_2S \cdot HI$:

18 C, 26.48; H, 4.81; N, 10.29; S, 11.78; I, 46.63;

19 Found: C, 26.29; H, 4.73; N, 10.39; S, 12.03; I, 47.01.

20 Step B: Preparation of 1-Ethyl-2-hydrazino-2-imidazoline
 21 hydriodide

22 1-Ethyl-2-methylthio-2-imidazoline hydriodide (15
 23 g., 0.055 mole) and hydrazine hydrate (5 g.) are reacted
 24 according to the procedure described in Example 37, Step A,
 25 yielding 8.6 g. (61%) of product, m.p. 98-99° C.

26 Analysis calculated for $C_{15}H_{12}N_4 \cdot HI \cdot C_2H_5OH$:

27 N, 18.54; I, 42.00;

28 Found: N, 18.69; I, 42.52.

29 Step C: Preparation of 1-(1-Ethyl-2-imidazolin-2-yl)-4-
 30 (4-pyridyl)-pyrazole dihydrochloride

31 1-Ethyl-2-hydrazino-2-imidazoline hydriodide (2.8
 32 g., 11 mmole) and 4-pyridylmalondialdehyde (1.5 g., 10 mmole)
 33 in 2% hydrochloric acid (50 ml.) are reacted according to

994338

1 the procedure described in Example 37, Step B, yielding 2.6
2 g. (93%) of product, m.p. 259-263° C.

3 Analysis calculated for $C_{13}H_{15}N_5 \cdot 2HCl$:

4 C, 49.69; H, 5.45; N, 22.29; Cl, 22.57;

5 Found: C, 49.83; H, 5.80; N, 22.28; Cl, 22.48.

6 By following the procedure described in Example
7 50, Steps A-D, with the exception the N-methylethylenedia-
8 mine is replaced by an equivalent quantity of

9 N-n-propylethylenediamine (Example 52),

10 N-isopropylethylenediamine (Example 53) and

11 N-(2-butyl)ethylenediamine (Example 54),

12 there is obtained, respectively:

13 EXAMPLE 52

14 1-(1-n-Propyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole
15 dihydrochloride

16 Step A: Preparation of 1-n-Propyl-2-imidazolidinethione

17 Yield, 85%; m.p. 88-89° C.

18 Analysis calculated for $C_6H_{12}N_2S$:

19 C, 49.96; H, 8.39; N, 19.42; S, 22.23;

20 Found: C, 49.95; H, 8.38; N, 19.69; S, 21.97.

21 Step B: Preparation of 1-n-Propyl-2-methylthio-2-imidazol-
22 ine hydriodide

23 Yield 82%; m.p. 118-121° C.

24 Analysis calculated for $C_7H_{14}N_2S \cdot HI$:

25 C, 29.38; H, 5.28; N, 9.79; S, 11.20; I, 44.34;

26 Found: C, 29.85; H, 5.04; N, 10.00; S, 11.50; I, 44.22.

27 Step C: Preparation of 1-n-Propyl-2-hydrazino-2-imidazol-
28 ine hydriodide

29 Yield 87%; m.p. 102° C.

30 NMR: ppm: 4.72 (2H, imidazoline protons); 3.18 t(2H,

31 CH_2 , J = 7 Hz); 2.65 sextuplet (2H, CH_2 ,

32 J = 7 Hz); 0.88 t(3H, CH_3 , J = 7 Hz).

994338

1 Step D: Preparation of 1-(1-n-Propyl-2-imidazolin-2-yl)-4-
2 (4-pyridyl)-pyrazole dihydrochloride

3 Yield 40%; m.p. 234-237° C. (dec.).

4 Analysis calculated for $C_{14}H_{17}N_5 \cdot 2HCl$:

5 C, 51.23; H, 5.83; N, 21.34; Cl, 21.60;

6 Found: C, 51.49; H, 5.63; N, 21.61; Cl, 21.70.

7 EXAMPLE 53

8 1-(1-Isopropyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole
9 dihydrochloride

10 Step A: Preparation of 1-Isopropyl-2-imidazolidinethione

11 Yield, 55%; m.p. 165-166° C.

12 Analysis calculated for $C_6H_{12}N_2S$:

13 C, 49.96; H, 8.39; N, 19.42; S, 22.23;

14 Found: C, 49.85; H, 8.45; N, 19.62; S, 22.40.

15 Step B: Preparation of 1-Isopropyl-2-methylthio-2-imidazol-
16 ine hydriodide

17 Yield, 83%; m.p. 139-141° C.

18 Analysis calculated for $C_7H_{14}N_2S \cdot HI$:

19 C, 29.38; H, 5.28; N, 9.79; S, 11.20; I, 44.34;

20 Found: C, 29.82; H, 5.12; N, 9.87; S, 11.43; I, 44.23.

21 Step C: Preparation of 1-Isopropyl-2-hydrazino-2-imidazol-
22 ine hydriodide

23 Yield, 90%; m.p. 48-57° C.

24 NMR: ppm: 3.80 septuplet (1H, CH, $J = 6$ Hz); 3.75 (2H,

25 imidazoline protons); 1.22 d(3H, CH_3 , $J = 6$

26 Hz).

27 Step D: Preparation of 1-(1-Isopropyl-2-imidazolin-2-yl)-4-
28 (4-pyridyl)-pyrazole dihydrochloride

29 Yield 45%; m.p. 256-258° C. (dec.).

30 Analysis calculated for $C_{14}H_{17}N_5 \cdot 2HCl$:

31 C, 51.23; H, 5.83; N, 21.34; Cl, 21.60;

32 Found: C, 51.45; H, 5.86; N, 21.71; Cl, 21.25.

994338

EXAMPLE 54

1-[1-(2-Butyl)-2-imidazolin-2-yl]-4-(4-pyridyl)-pyrazole dihydrochloride

Step A: Preparation of 1-(2-Butyl)-2-imidazolidinethione

Yield, 65%; m.p. 155-156° C.

Analysis calculated for $C_7H_{14}N_2S$:

C, 53.12; H, 8.92; N, 17.70; S, 20.26;

Found: C, 52.96; H, 8.69; N, 18.00; S, 20.37.

Step B: Preparation of 1-(2-Butyl)-2-methylthio-2-imidazoline hydriodide

Yield, 86%; m.p. 110-112° C.

Analysis calculated for $C_8H_{16}N_2S \cdot HI$:

C, 32.01; H, 5.70; N, 9.33; S, 10.68; I, 42.27;

Found: C, 31.83; H, 5.46; N, 9.51; S, 10.98; I, 42.53.

Step C: Preparation of 1-(2-Butyl)-2-hydrazino-2-imidazoline hydriodide

Yield, 85%; as thick yellow oil.

NMR: ppm: 3.70 (2H, imidazoline protons); 3.60 sextuplet

(2H, CH, $J = 7$ Hz); 1.65 quintuplet (2H, CH_2 ,

$J = 7$ Hz); 1.20 d(3H, CH_3 , $J = 7$ Hz); 0.85

t(3H, CH_3 , $J = 7$ Hz).

Step D: Preparation of 1-[1-(2-Butyl)-2-imidazolin-2-yl]-4-(4-pyridyl)-pyrazole dihydrochloride

Yield, 28%, m.p. 257-259° C.

Analysis calculated for $C_{15}H_{19}N_5 \cdot 2HCl$:

C, 52.63; H, 6.18; N, 20.46; Cl, 20.72;

Found: C, 52.51; H, 6.38; N, 20.47; Cl, 20.61.

EXAMPLE 55

1-Methyl-5-phenyl-4-(4-pyridyl)-pyrazole

To a mixture of 1-methyl-4-(4-pyridyl)-5-amino-pyrazole (870 mg., 5 mmole), (Example 6 product) acetic anhydride (1.53 g., 15 mmole), anhydrous potassium acetate (500 mg., 5.1 mmole) and benzene (15 ml.) stirred under

994338

1 reflux is added dropwise over one hour a solution of isoamyl
2 nitrite (1.0 ml., 880 mg., 7.5 mmole) in benzene (5 ml.).
3 The mixture is heated under reflux for 22 hours, cooled to
4 room temperature and diluted with more benzene (15 ml.).
5 Chromatographic grade silica gel (4 g.) is added and the
6 solvent is evaporated under reduced pressure. The residue
7 is placed at the top of a column of silica gel (80 g.) and
8 developed by the dry column technique with ethyl acetate.
9 After a small two component eluate, the product is collec-
10 ted. Evaporation of the solution affords 522 mg. (42%) of
11 brown oil, which soon solidifies. Recrystallization of the
12 crude base from di-isopropyl ether (charcoal) gives the pro-
13 duct in the form of colorless needles, m.p. 129-129.5° C.

14 Analysis calculated for $C_{15}H_{13}N_3$:
15 C, 76.57; H, 5.57; N, 17.86;
16 Found: C, 76.60; H, 5.62; N, 18.02.

17 EXAMPLE 56

18 1-Methyl-4-(4-pyridyl)-5-(2-furyl)-pyrazole

19 Replacing benzene in Example 55 with furan as
20 solvent and reactant and following substantially the same
21 procedure there is obtained 1-methyl-4-(4-pyridyl)-5-(2-
22 furyl)-pyrazole which can be isolated by chromatography and
23 purified by recrystallization from di-isopropyl ether.

24 EXAMPLE 57

25 1-(1-Ethyl-2-imidazolin-2-yl)-3-methyl-4-(4-pyridyl)-5-amino-pyrazole

26 By replacing, in Example 44, aminoguanidine bicar-
27 bonate with an equimolecular quantity of 1-ethyl-2-hydrazino-
28 2-imidazoline hydriodide and replacing 2-formyl-2-(4-pyri-
29 dyl)-acetonitrile with an equimolecular amount of 2-acetyl-
30 2-(4-pyridyl)-acetonitrile and using 100 ml. of 0.5N hydro-
31 chloric acid in place of 100 ml. of 1N hydrochloric acid,

994338

1 there is obtained 1-(1-ethyl-2-imidazolin-2-yl)-3-methyl-4-
2 (4-pyridyl)-5-amino-pyrazole.

3 EXAMPLE 58

4 1,3-Dimethyl-4-(4-pyridyl)-5-amino-pyrazole

5 By replacing 2-formyl-2-(4-pyridyl)-acetonitrile
6 in Example 6 with an equivalent amount of 2-acetyl-2-(4-
7 pyridyl)-acetonitrile there is obtained 1,3-dimethyl-4-(4-
8 pyridyl)-5-amino-pyrazole which is isolated as the hydro-
9 chloride salt and purified by recrystallization from
10 ethanol.

11 EXAMPLE 59

12 1,3-Dimethyl-4-(4-pyridyl)-5-(1-pyrrolyl)-pyrazole

13 By replacing 1-methyl-4-(4-pyridyl)-5-amino-pyra-
14 zole in Example 55 with 1,3-dimethyl-4-(4-pyridyl)-5-amino-
15 pyrazole (Example 58 product) there is obtained 1,3-dimethyl-
16 4-(4-pyridyl)-5-(1-pyrrolyl)-pyrazole conveniently isolated
17 as the hydrochloride salt and purified by recrystallization
18 from isopropanol.

19 EXAMPLE 60

20 1-(1-Ethyl-2-imidazolin-2-yl)-4-(4-pyridyl)-5-amino-
21 pyrazole maleate

22 A mixture of 1-ethyl-2-hydrazino-2-imidazoline
23 hydriodide (3.05 g., 11.8 mmole), 2-formyl-2-(4-pyridyl)-
24 acetonitrile (1.73 g., 11.8 mmole) and N hydrochloric acid
25 (11.8 ml.) is warmed on a steam bath with stirring until a
26 solution is obtained. The solution is allowed to stand at
27 ambient temperature for 4 hours, then it is made basic with
28 5N sodium hydroxide solution and extracted with ethyl ace-
29 tate (3 x 19 ml.). The extract is washed with a little
30 saturated sodium chloride solution, dried over magnesium
31 sulfate and evaporated to a reddish-brown oil, 2.95 g. (97%).

994338

1 The oil is treated with hot isopropanol (five parts volume
2 by weight) containing an equimolar amount of maleic acid.
3 When cool, the solid is collected and washed with a little
4 isopropanol to afford 80% of 1-(1-ethyl-2-imidazolin-2-yl)-
5 4-(4-pyridyl)-5-amino-pyrazole hydrogen maleate, m.p. 142-
6 145° C. (dec.).

7 Analysis calculated for $C_{13}H_{16}N_6 \cdot C_4H_4O_4$:
8 C, 52.30; H, 5.68; N, 21.53;
9 Found: C, 52.52; H, 5.35; N, 21.18.

10 EXAMPLE 61

11 1-Methyl-4-(4-pyridyl)-5-(2,5-dimethylpyrrol-1-yl)-
12 pyrazole hydrochloride

13 Replacement of 2,5-dimethoxy-tetrahydrofuran in
14 Example 48 with an equivalent amount of 2,5-hexanedione and
15 extending the heating under reflux from 30 to 90 minutes
16 affords 47% of 1-methyl-4-(4-pyridyl)-5-(2,5-dimethylpyrrol-
17 1-yl)-pyrazole hydrochloride after the appropriate work-up
18 as described in Example 48. The compound crystallizes from
19 isopropanol in pale cream needles, m.p. 259-261° C. (dec.).

20 Analysis calculated for $C_{15}H_{16}N_4 \cdot HCl$:
21 C, 62.39; H, 5.93; Cl, 12.28; N, 19.40;
22 Found: C, 62.63; H, 5.61; Cl, 12.17; N, 19.70.

23 EXAMPLE 62

24 1-Methyl-4-(4-pyridyl)-5-ethylamino-pyrazole hydrochloride

25 To a slurry of lithium aluminum hydride (1.28 g.,
26 34 mmole) in tetrahydrofuran (70 ml.) under dry nitrogen is
27 added 1-methyl-4-(4-pyridyl)-5-acetamido-pyrazole (Example
28 11) (4.9 g., 22.5 mmole) in small portions and with stirring.
29 Then the mixture is stirred at 45-50° C. for 3 hours, and
30 cooled to ambient temperature. Excess hydride is decom-
31 posed by the successive addition of water (1.3 ml.), 10%

994338

1 sodium hydroxide solution (1.95 ml.) and water (3.4 ml.).
2 The metal hydroxides are filtered off and the filtrate evap-
3 orated to an oil. Additional product is obtained by dissolv-
4 ing the solids in 5N sodium hydroxide solution and extract-
5 ing the solution with ether. The combined crude base is
6 dissolved in isopropanol and a slight excess of ethanolic
7 hydrogen chloride solution added to give 1-methyl-4-(4-pyri-
8 dyl)-5-ethylamino-pyrazole hydrochloride, 1.95 g. (36%),
9 m.p. 257-260° C. Following recrystallization from isopro-
10 panol the product has m.p. 258-261° C.

11 Analysis calculated for $C_{11}H_{14}N_4 \cdot HCl$:
12 C, 55.34; H, 6.33; Cl, 14.85; N, 23.47;
13 Found: C, 55.20; H, 6.22; Cl, 15.06; N, 23.60.

14 EXAMPLE 63

15 3(5)-Chloro-4-(4-pyridyl)-pyrazole
16 3(5)-Amino-4-(4-pyridyl)-pyrazole (1.60 g., 10
17 mmole) (Example 7 product) is suspended in 5N hydrochloric
18 acid (10 ml.) and to the cooled suspension at 0-5° C. is
19 added finely powdered sodium nitrite (690 mg., 10 mmole) in
20 small portions and with stirring. The mixture is stirred
21 at 0-5° C. for 30 minutes and then neutralized with 5N sod-
22 ium hydroxide solution to afford 3(5)-chloro-4-(4-pyridyl)-
23 pyrazole, 1.24 g. (69%). Recrystallization of the product
24 from water gives analytically pure compound, m.p. 189-191°
25 C.

26 Analysis calculated for $C_8H_6ClN_3$:
27 C, 53.49; H, 3.37; Cl, 19.74; N, 23.39;
28 Found: C, 53.27; H, 3.52; Cl, 19.72; N, 23.12.

29 EXAMPLE 64

30 1-(N,N-Dimethylamidino)-4-(4-pyridyl)-5-amino-pyrazole
31 hydrochloride

32 To a suspension of 2-formyl-2-(4-pyridyl)-aceto-

994338

1 nitrile (from Example 6) (12.4 g., 85 mmole) in N hydrochlor-
2 ic acid (85 ml.) is added dimethylaminoguanidine hydriodide
3 (19.5 g., 85 mmole) and the mixture is heated at about 80° C.
4 for one hour, then kept at ambient temperature for 3 hours,
5 filtered and the filtrate made basic with 5N sodium hydroxide
6 solution and immediately extracted with ethyl acetate (100
7 ml.). The aqueous phase is extracted with methylene chloride
8 (5 x 100 ml.) affording 12 g. of crude oily 1-(N,N-dimethyl-
9 amidino)-4-(4-pyridyl)-5-amino-pyrazole. The crude base is
10 converted to a crystalline hydrochloride by dissolving the oil
11 (2.3 g.) in isopropanol (30 ml.) and adding ethanolic hydrogen
12 chloride solution. Melting point of hydrochloride, 205-206°C.

13 Analysis calculated for $C_{11}H_{14}N_6 \cdot HCl \cdot 1/2 H_2O$:

14 C, 47.91; H, 5.85; Cl, 12.85; N, 30.47;

15 Found: C, 48.17; H, 5.46; Cl, 12.83; N, 30.60.

16 EXAMPLE 65

17 3-(4-Pyridyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrimidin-5-one

18 A mixture of 3(5)-amino-4-(4-pyridyl)-pyrazole,
19 Example 7 product, (9.6 g., 60 mmole), ethyl acrylate (6.6
20 g., 66 mmole), triton B (40% solution of benzyl trimethyl-
21 ammonium hydroxide in methanol) (12 drops) and n-butanol
22 (120 ml.) is heated under reflux for 3 days. On cooling
23 the solution, 2.35 g. (18%) of 3-(4-pyridyl)-6,6-dihydro-
24 4H-pyrazolo[1,5-a]pyrimidin-5-one, m.p. 268-270°, crystal-
25 lizes out. Recrystallization of the product from alcohol
26 raised the melting point to 270-272° C.

27 Analysis calculated for $C_{11}H_{10}N_4O$:

28 C, 61.67; H, 4.70; N, 26.15;

29 Found: C, 61.84; H, 5.00; N, 26.30.

30 EXAMPLE 66

31 3-(4-Pyridyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrimidine

32 To a slurry of lithium aluminum hydride (569 mg.,

994338

1 15 mmole) in dry tetrahydrofuran (35 ml.) stirred under nitro-
2 gen is added 3-(4-pyridyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyr-
3 imidin-5-one, Example 65 product, (2.78 g., 13 mmole) in small
4 portions. The mixture is stirred under reflux overnight, then
5 the excess hydride is destroyed by cautious addition of water
6 (0.6 ml.), followed by 10% sodium hydroxide solution (1 ml.)
7 and more water (1.7 ml.). The tetrahydrofuran solution is fil-
8 tered and evaporated to afford 700 mg. of solid. More product
9 is isolated by dissolving the metal hydroxides in 5N sodium hy-
10 droxide solution and extracting with methylene chloride provid-
11 ing an overall yield of 1.139 g. (43%). Recrystallization of the
12 crude product from benzene gives pure compound, m.p. 166-168° C.

13 Analysis calculated for $C_{11}H_{12}N_4$:

14 C, 65.98; H, 6.04; N, 27.98;

15 Found: C, 65.83; H, 6.33; N, 27.53.

16 EXAMPLE 67

17 3-(4-Pyridyl)-4-methyl-4,5,6,7-tetrahydro-pyrazolo-
18 [1,5-a]pyrimidine

19 A mixture of 3-(4-pyridyl)-4,5,6,7-tetrahydro-
20 pyrazolo[1,5-a]pyrimidine, Example 66 product, (700 mg.,
21 3.49 mmole), 98% formic acid (1 ml.), and formaldehyde solu-
22 tion (2 ml.) is heated under reflux for 24 hours. The mix-
23 ture is evaporated to dryness and the residue treated with
24 isopropanol (20 ml.). Addition of a slight excess of
25 ethanolic hydrogen chloride solution causes the crystalli-
26 zation of 3-(4-pyridyl)-4-methyl-4,5,6,7-tetrahydro-pyra-
27 zolo[1,5-a]pyrimidine hydrochloride, 485 mg., (65%). Re-
28 crystallization of the solid from ethanol (ca. 4 ml.) af-
29 fords pure compound, m.p. 241-243° C.

30 Analysis calculated for $C_{12}H_{14}N_4 \cdot 2HCl$:

31 C, 50.18; H, 5.61; Cl, 24.69; N, 19.50;

32 Found: C, 50.45; H, 6.02; Cl, 24.66; N, 19.67.

994338

EXAMPLE 683(5)-Methyl-4-(4-pyridyl)-pyrazoleStep A: Preparation of 4-Pyridylacetone

4-Picoline (93 g., 1 mole) is added to a suspension of sodium amide prepared from sodium (23 g., 1 mole) in 600 ml. anhydrous liquid ammonia. The mixture is stirred for 15 to 20 minutes. To the suspension of 4-picolyne, sodium ethyl acetate (66 g., 0.75 mole) is added over a period of 30 minutes and stirring continued for an extra hour. The reaction is quenched by addition of excess solid ammonium chloride and the liquid ammonia replaced by adding ether and warming on a water bath. When the ammonia evaporates, the reaction mixture is poured onto a mixture of ice and hydrochloric acid. The ether is decanted, the aqueous solution made basic and extracted with ether. The organic layer is washed with water, dried over magnesium sulfate and concentrated under vacuum, leaving a residue that is distilled at 70-75° C. at 1 mm. yielding 4-pyridyl acetone (5 g., 5%).

Step B: Preparation of 3(5)-Methyl-4-(4-pyridyl)-pyrazole

4-Pyridylacetone (135 mg., 1 mmole), ethyl formate (75 mg., 1 mmole), sodium ethoxide (100 mg., 1.5 mmole) are refluxed in benzene for 18 hours. The brownish solid is filtered off, dissolved in water, acidified with 10% hydrochloric acid and hydrazine hydrate is added (50 mg., 1 mmole). The solution is heated on the steam bath for 1 hour, then cooled to ambient temperature, made basic with 10% sodium hydroxide and extracted with ethyl acetate. The organic layer is washed with water until neutral and dried over magnesium sulfate. The evaporation of the solvent left 89 mg. of a yellow oil, identified as 3(5)-methyl-4-(4-pyridyl)-pyrazole by its NMR spectrum in dilute DCl.

994338

1 NMR: ppm: 8.92 d(J = 6 Hz, α -pyridyl proton); 8.20
2 d(J = 6 Hz; β -pyridyl proton); 7.98 s(pyra-
3 zole proton); 2.45 s(CH₃).

4 EXAMPLE 69

5 3,5-Dimethyl-4-(4-pyridyl)-pyrazole

6 This product is obtained by replacing ethyl for-
7 mate employed in Step B of Example 68 by an equivalent quan-
8 tity of ethyl acetate and otherwise following substantially
9 the same procedure.

10 Other 3,5-dialkyl-4-(4-pyridyl)-pyrazole compounds
11 can similarly be prepared by employing the appropriate alkyl
12 ester of an alkanolic acid.

13 EXAMPLE 70

14 1,3,5-Trimethyl-4-(4-pyridyl)-pyrazole

15 This product is prepared by replacing ethyl for-
16 mate and hydrazine employed in Step B of Example 68 by
17 equivalent quantities of ethyl acetate and methyl-hydrazine,
18 respectively, and otherwise following substantially the same
19 procedure.

20 Other 1-R³-3,5-dialkyl-4-(4-pyridyl)-pyrazoles can
21 similarly be prepared by employing the appropriate alkyl
22 ester of an alkanolic acid and an H₂N-NHR³ wherein R³ is the
23 desired 1-position substituent group.

24 EXAMPLE 71

25 1-(2-Imidazolin-2-yl)-3,5-dimethyl-4-(4-pyridyl)-pyrazole

26 This product is prepared by replacing ethyl for-
27 mate and hydrazine employed in Step B of Example 68 by
28 equivalent quantities of ethyl acetate and 2-imidazol-2-
29 ylhydrazine, respectively, and otherwise following substan-
30 tially the same procedure.

994338

1 EXAMPLE 72

2 1,3(5)-Dimethyl-4-(4-pyridyl)-pyrazole

3 These compounds are prepared by replacing the
4 hydrazine employed in Step B of Example 68 by an equivalent
5 quantity of methyl-hydrazine and otherwise following substan-
6 tially the same procedure.

7 EXAMPLE 73

8 1-Methyl-4-(4-pyridyl)-5-isopropoxy-pyrazole

9 A mixture of 1-methyl-4-(4-pyridyl)-5-hydroxy-
10 pyrazole (prepared as described in Example 9) (10 mmole),
11 sodium carbonate (11 mmole), isopropyl iodide (13.3 mmole)
12 and sodium iodide in dimethylformamide (25 ml.) is heated
13 at 55-60° C. for about 1/2 hour with stirring. The reaction
14 mixture is quenched with water (ca. 150 ml.) and then ex-
15 tracted with 3 x 25 ml. ether. The ether extracts are com-
16 bined, dried over magnesium sulfate and concentrated to dry-
17 ness yielding 1-methyl-4-(4-pyridyl)-5-isopropoxy-pyrazole.

18 EXAMPLE 74

19 1-Methyl-4-(3-n-propoxy-4-pyridyl)-pyrazole

20 This product is prepared by replacing the 1-methyl-
21 4-(4-pyridyl)-5-hydroxy-pyrazole and the isopropyl iodide
22 employed in Example 73 by equivalent quantities of 1-methyl-
23 4-(3-hydroxy-4-pyridyl)-pyrazole (prepared as described in
24 Example 19) and n-propyl iodide, respectively, and otherwise
25 following substantially the same procedure.

26 Other 4-(4-pyridyl)-5-alkoxy-pyrazoles and other
27 4-(3-alkoxy-4-pyridyl)-pyrazoles can be prepared by the
28 methods described in Examples 73 and 74 by employing the
29 appropriate alkyl halide.

30 Other known 4-(4-pyridyl)-pyrazole compounds that
31 have been found to be effective bronchodilating agents in

994338


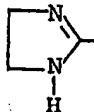

1 the method of this invention are:

2 4-(4-pyridyl)-pyrazole and
3 1-carbamoyl-4-(4-pyridyl)-pyrazole.

4 The products of this invention were found, when
5 tested according to standard protocols in anesthetized dogs,
6 to inhibit bronchial constriction induced by one or more
7 bronchoconstrictor agonists; known procedures for evaluat-
8 ing bronchodilating properties of products. In addition,
9 certain compounds were also found to exhibit hypotensive
10 properties, probably due to their actions as peripheral vaso-
11 dilators, and are therefore of potential use as antihyper-
12 tensive drugs.

13 The dose of representative products which was
14 required to inhibit histamine induced bronchial constrict-
15 tion in anesthetized dogs at the ED₅₀ level when tested by
16 the above procedure is provided in the following table.
17 It will be noted that the test data establishes that the
18 compounds are generally more effective bronchial dilating
19 agents than the control drug, theophylline. Because of this
20 high order of activity, the active ingredients of the claimed
21 method and formulations are useful in the management of
22 asthma, allergic reactions and other disorders associated
23 with or resulting from bronchial constriction.

994338

TABLE I						
COMPOUND						
Structure I					ED ₅₀	
Ex. No.	R ¹	R ²	R ³	R ⁴	mg./kg.	
THEOPHYLLINE					64.5	
12	H	(CH ₃) ₂ N-	CH ₃ -	H	9.0	
11	H	CH ₃ CONH-	CH ₃ -	H	50.0	
4	H	H	CH ₂ =CH-CH ₂ -	H	13.0	
24	H	H	CH ₃ OCH ₂ CH ₂ -	H	20.0	
27	H	H	 -CH ₂ CH ₂ -	H	72.0	
(p. 44)	H	H	H	H	9.0	
35	H	H	H ₂ N-C(=NH)-	H	15.0	
35	H	H	isethionate of above	H	15.0	
3	H	H	(CH ₃) ₂ CHCH ₂ -	H	14.0	
37	H	H		H	10.0	
31	H	H	(CH ₃) ₂ NCO-	H	6.0 & 8.0	
51	H	H		H	25.0	

While the invention has been illustrated by certain specific members of the 4-(4-pyridyl)-pyrazole products made by certain specific methods and formulated into certain specific dosage forms, it is to be understood that the invention is not to be considered limited by or to the specific

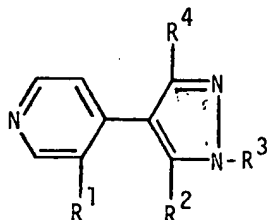
994338

1 embodiments illustrated but is to encompass other members
2 of the products falling within the scope of the generic
3 disclosure and claims as well as other methods or modifi-
4 cations of the methods described for their preparation,
5 administration and formulations, all of which would be
6 obvious in view of the teaching herein to one skilled in
7 the art.

994338

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. The process for preparing a 4-(4-pyridyl)-pyrazole of the formula:

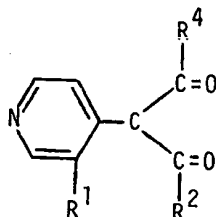


wherein R^1 represents hydrogen, nitro, amino, acetamino, mono- or di-alkylamino, cyano, phenyl, hydroxy, alkoxy, or halo, preferably chloro; R^2 represents hydrogen, halogen, preferably chloro, alkyl, hydroxy, alkoxy, cyano, amino, acetamino, mono- or di-alkylamino, phenyl, furyl, 4-pyridyl, 1-pyrrolyl or mono- or di- C_{1-3} alkyl-1-pyrrolyl; R^3 represents hydrogen, alkyl either straight or branched chain and having from 1-5 carbon atoms, alkenyl, alkynyl, C_{3-10} cycloalkyl, preferably adamantyl, haloalkyl, preferably polyfluoroalkyl, alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl, (4-pyridyl)- C_{1-3} alkyl, alkoxycarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, 4-alkylpiperazinylcarbonyl, piperidinocarbonyl, N-alkylthiocarbamoyl, phenyl, amidino or mono- or di-alkyl substituted amidino, 2-imidazolin-2-yl or 1- C_{1-5} alkyl substituted 2-imidazolin-2-yl, 2-, 3- or 4-pyridyl, 2-(3,4,5,6-tetrahydropyrimidinyl), 2-(3,4-dihydro-1,3-thiazolyl), and 2-(5,6-dihydro-4(H)-1,3-thiazinyl); R^2 and R^3 can be linked together to form with the pyrazolo nucleus to which they are attached a 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl, a 4- C_{1-3} alkyl substituted 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl or a 6,7-dihydro-5(4H)-oxopyrazolo[1,5-a]pyrimidin-3-yl; and R^4

represents hydrogen and C_{1-3} alkyl, with the proviso that R^2 , R^3 and R^4 are not hydrogen at the same time and that when R^3 is carbamoyl, R^2 and R^4 may not be hydrogen,

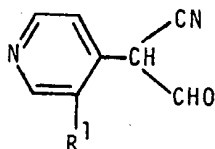
which comprises

- A. when R^3 is other than NH_2 : reacting a dicarbonyl compound of the formula:



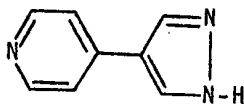
with a hydrazine of the formula H_2NNHR^3 , wherein R^1 , R^2 , R^3 and R^4 are as previously defined; or

- B. when R^3 is NH_2 and R^4 is hydrogen: reacting a 2-formyl-2-(4-pyridyl)acetonitrile of the formula:



with a hydrazine of the formula H_2NNHR^3 , R^1 being as defined previously, and R^3 being defined as previously except that it is other than hydrogen; or

- C. when R^3 is to be alkyl of 1 to 5 carbon atoms: alkylating a 4-(4-pyridyl)pyrazole of the formula:



with an alkyl halide.

2. The process of Step A of Claim 1, wherein 4-pyridylmalondialdehyde is reacted with methoxyethylhydrazine to form the 1-(2-methoxyethyl)-4-(4-pyridyl)pyrazole.

994338

3. The process of Step A of Claim 1, wherein 4-pyridylmalondialdehyde is reacted with 4,4-dimethylsemicarbazide to form the 1-dimethylcarbamoyl-4-(4-pyridyl)pyrazole.

4. The process of Step A of Claim 1, wherein 4-pyridylmalondialdehyde is reacted with aminoguanidine bicarbonate to form the 1-amidino-4-(4-pyridyl)pyrazole.

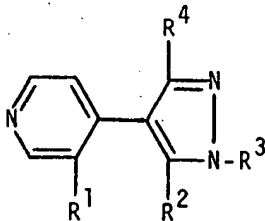
5. The process of Step A of Claim 1, wherein 4-pyridylmalondialdehyde is reacted with 1-ethyl-2-hydrazino-2-imidazoline to form the 1-(1-ethyl-2-imidazolin-2-yl)-4-(4-pyridyl)pyrazole.

6. The process of Step B of Claim 1, wherein 2-formyl-2-(4-pyridyl)acetonitrile is reacted with methylhydrazine to form the 1-methyl-4-(4-pyridyl)-5-amino-pyrazole.

7. The process of Claim 6, comprising the further step of reacting the 1-methyl-4-(4-pyridyl)-5-amino-pyrazole with acetic anhydride to form the 1-methyl-4-(4-pyridyl)-5-acetamido-pyrazole.

8. The process of Claim 6, comprising the further step of reacting the 1-methyl-4-(4-pyridyl)-5-amino-pyrazole with a formaldehyde-formic acid mixture to form the 1-methyl-4-(4-pyridyl)-5-dimethylamino-pyrazole.

9. The 4-(4-pyridyl)pyrazole of the formula:



994338

wherein R^1 represents hydrogen, nitro, amino, acetamino, mono- or di-alkylamino, cyano, phenyl, hydroxy, alkoxy, or halo, preferably chloro; R^2 represents hydrogen, halogen, preferably chloro, alkyl, hydroxy, alkoxy, cyano, amino, acetamino, mono- or di-alkylamino, phenyl, furyl, 4-pyridyl, 1-pyrrolyl or mono- or di- C_{1-3} alkyl-1-pyrrolyl; R^3 represents hydrogen, alkyl either straight or branched chain and having from 1-5 carbon atoms, alkenyl, alkynyl, C_{3-10} cycloalkyl, preferably adamantyl, haloalkyl, preferably polyfluoroalkyl, alkoxyalkyl, hydroxyalkyl, dialkylaminoalkyl, (4-pyridyl)- C_{1-3} alkyl, alkoxycarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, 4-alkylpiperazinylcarbonyl, piperidinocarbonyl, N-alkylthiocarbamoyl, phenyl, amidino or mono- or di-alkyl substituted amidino, 2-imidazolin-2-yl or 1- C_{1-5} alkyl substituted 2-imidazolin-2-yl, 2-, 3- or 4-pyridyl, 2-(3,4,5,6-tetrahydropyrimidinyl), 2-(3,4-dihydro-1,3-thiazolyl), and 2-(5,6-dihydro-4(H)-1,3-thiazinyl); R^2 and R^3 can be linked together to form with the pyrazolo nucleus to which they are attached a 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl, a 4- C_{1-3} alkyl substituted 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl or a 6,7-dihydro-5(4H)-oxypyrazolo[1,5-a]pyrimidin-3-yl; and R^4 represents hydrogen and C_{1-3} alkyl, with the proviso that R^2 , R^3 and R^4 are not hydrogen at the same time and that when R^3 is carbamoyl, R^2 and R^4 may not be hydrogen, when prepared by the process defined in Claim 1 or by an obvious chemical equivalent.

10. The 1-(2-methoxyethyl)-4-(4-pyridyl)pyrazole, when prepared by the process defined in Claim 2 or by an obvious chemical equivalent.

994338

11. The 1-dimethylcarbamoyl-4-(4-pyridyl)pyrazole, when prepared by the process defined in Claim 3 or by an obvious chemical equivalent.

12. The 1-amidino-4-(4-pyridyl)pyrazole, when prepared by the process defined in Claim 4 or by an obvious chemical equivalent.

13. The 1-(1-ethyl-2-imidazolin-2-yl)-4-(4-pyridyl)-pyrazole, when prepared by the process defined in Claim 5 or by an obvious chemical equivalent.

14. The 1-methyl-4-(4-pyridyl)-5-amino-pyrazole, when prepared by the process defined in Claim 6 or by an obvious chemical equivalent.

15. The 1-methyl-4-(4-pyridyl)-5-acetamido-pyrazole, when prepared by the process defined in Claim 7 or by an obvious chemical equivalent.

16. The 1-methyl-4-(4-pyridyl)-5-dimethylamino-pyrazole, when prepared by the process defined in Claim 8 or by an obvious chemical equivalent.

A

SUBSTITUTE
REMPLACEMENT

SECTION is not Present
Cette Section est Absente